A. M. A.

AMERICAN JOURNAL OF

DISEASES of CHILDREN

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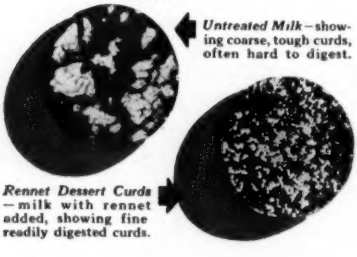

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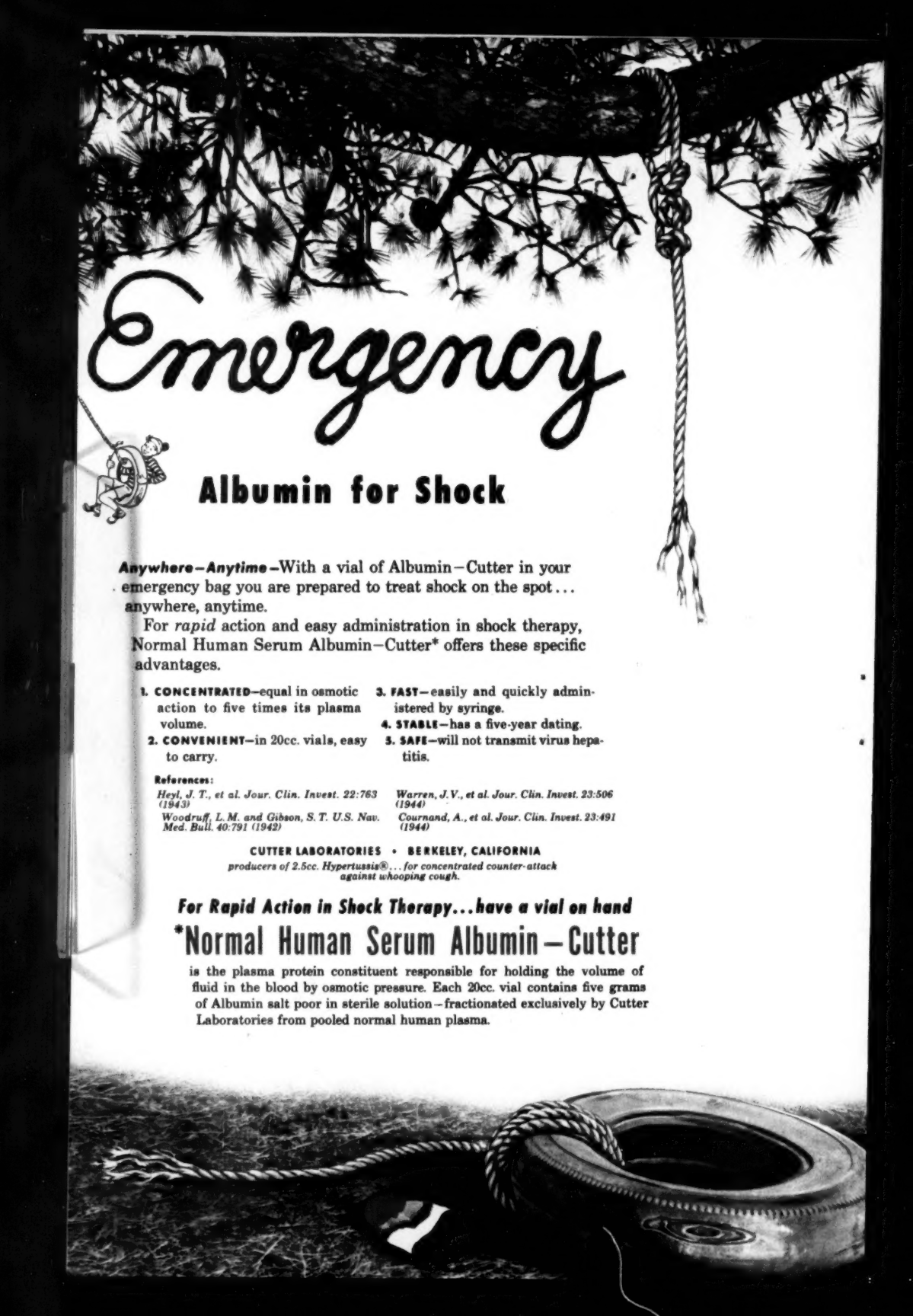

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Woodruff, L. M. and Gibson, S. T. U.S. Nav. Med. Bull. 40:791 (1942)

Warren, J. V., et al. Jour. Clin. Invest. 23:506 (1944)

Cournand, A., et al. Jour. Clin. Invest. 23:491 (1944)

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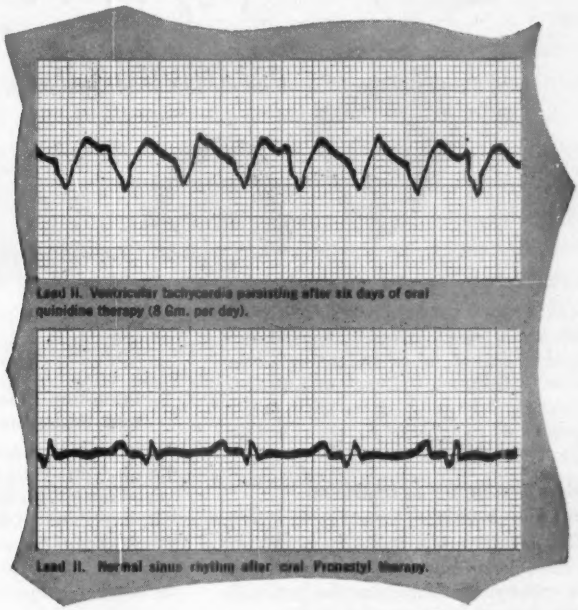

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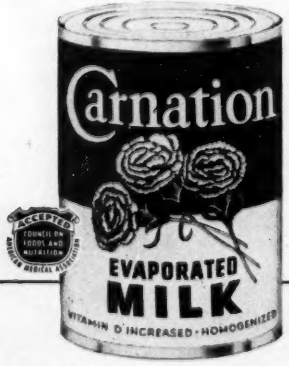

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MEAT...and the PROTEIN NEEDS of the DIABETIC

Not less but *more protein* than the traditional gram per kilo of body weight recommended for the non-diabetic individual promotes an increased sense of well-being in the diabetic patient. Liberal amounts of biologically excellent protein, such as that provided by *meat,* are therefore especially useful in dietotherapy.

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---

(1) Mosenthal, H. O.: Management of Diabetes Mellitus: An Analysis of Present-Day Methods of Treatment, Ann. Int. Med., 29:79 (July) 1948.

(2) McLester, J. S.: Nutrition and Diet in Health and Disease, 5th ed., Phil., W. B. Saunders Company, 1949, page 364.

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"excellent" response
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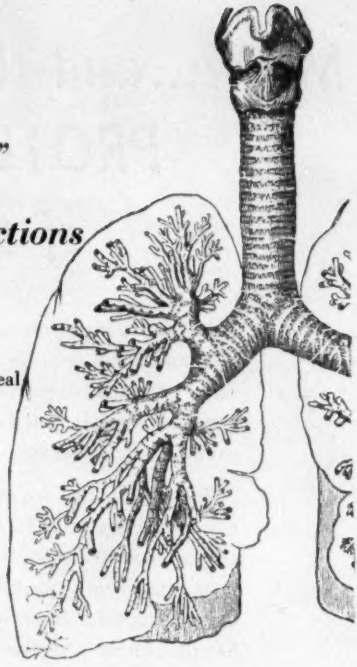
in acute upper respiratory infections



Promptness of response to therapy is essential in these infections to accelerate the patient's recovery and prevent the spreading of infection. Acute laryngotracheal bronchitis (H. influenzae)[1], acute follicular tonsillitis (Str. pyogenes)[2], and streptococcic pharyngitis[3,4] are among the conditions in which uniformly favorable responses described as "excellent" and "prompt" have been obtained with this new antibiotic agent. In pharyngitis particularly, it has been noted that Terramycin "...given orally appears to be extremely effective."[5]

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1. *Herrell, W. E.; Heilman, F. R., and Wellman, W. E.: Ann. New York Acad. Sc. 53:448 (Sept. 15) 1950.*
2. *Herrell, W. E.; Heilman, F. R.; Wellman, W. E., and Bartholomew, L. A.: Proc. Staff Meet. Mayo Clin. 25:183 (Apr. 12) 1950.*
3. *Knight, V.: New York State M. J. 50:2173 (Sept. 15) 1950.*
4. *Dowling, H. F.; Lepper, M. H.; Caldwell, E. R., and Spies, H. W.: Ann. New York Acad. Sc. 53:433 (Sept. 15) 1950.*
5. *Schenck, H. P.: M. Clin. North America 34:1621 (Nov.) 1950.*

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does not interfere with digestive process	☑	☐	☐
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1. Clinical Nutrition: ed. by N. Jolliffe et al., Hoeber, 1950. 2. Hanke M. T.: Diet and Dental Health, Chicago Univ. Press, 1933. 3. Jeans, P. C.: J.A.M.A., 142:806, 1950. 4. Joslin C. L. and Bradley, J. E.: Personal communication. 5. Krehl, W. A. and Cowgill, G. R.: Food Research, 15:179, 1950. 6. McLester, J. S.: Nutrition and Diet in Health and Disease, Saunders, Phila., 4th ed., 1944. 7. Moore, E. L. et al.: J. Home Econ., 37:290, 1945. 8. Roy, W. R. and Russell, H. E.: Food Industries, 20:1764, 1948. 9. Sherman, H. C.: Chemistry of Food and Nutrition, Macmillan, 7th ed., 1946. 10. Silverman, A. C.: New York J. Med., 47:1987, 1947. 11. Stevenson, S. S.: J. Pediat., 31:616, 1947.

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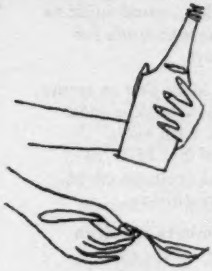

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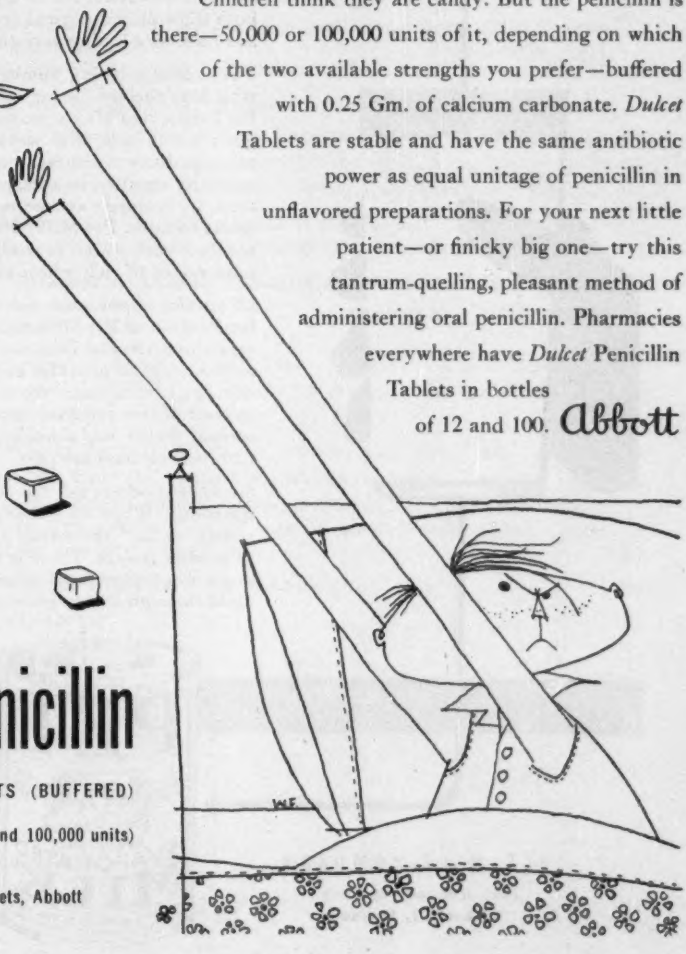

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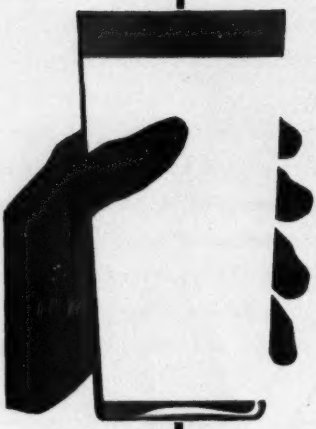

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CONTENTS

PAGE

Congenital Pulmonary Stenosis: Postoperative Observations on Two Hundred and Fourteen Children. C. R. Leininger, M.D., San Rafael, Calif.; Stanley Gibson, M.D., and Willis J. Potts, M.D., Chicago 465

Care, Feeding and Fate of Premature and Full Term Infants Born of Tuberculous Mothers. Bret Ratner, M.D., New York; Alexander E. Rostler, M.D., Fall River, Mass., and Pierre S. Salgado, M.D., Port-Au-Prince, Haiti 471

Immunization in the Young Infant: Response to Combined Vaccines:

I-IV. J. Cyril Peterson, M.D., and Amos Christie, M.D., Nashville, Tenn. 483

V. Amos Christie, M.D., and J. Cyril Peterson, M.D., Nashville, Tenn. 501

VI-X. J. Cyril Peterson, M.D., and Amos Christie, M.D., Nashville, Tenn. 518

Use of an Antihistaminic Drug for Treatment of the Common Cold at a Summer Camp for Boys. Peter Fisher, M.D., Sayre, Pa. 530

Staphylococcic Infections in Hospital Nurseries and Pediatrics Wards. Joseph Felsen, M.D.; Joseph Lapin, M.D.; William Wolarsky, M.D.; Alfred J. Weil, M.D., and Irving Fox, M.D., New York 534

Simplified Transparent Tuberculin Patch Test. Hermann Vollmer, M.D., New York, and David R. Lyons, M.D., East Orange, N. J. 541

CASE REPORTS:

Congenital Web of the Larynx. Phoebe Hudson, M.D., New York 545

Sudden Death of a Child Due to Carditis. Harold Gold, M.D., Toronto, Canada 550

Treatment of Toxic Diffuse Goiter (Graves's Disease) in Childhood: Report of a Case Successfully Treated with Propylthiouracil. Anne Topper, M.D., New York 556

ABSTRACTS FROM CURRENT LITERATURE 563

NEWS AND COMMENT 603

BOOK REVIEWS 604

DIRECTORY OF PEDIATRIC SOCIETIES 607

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CONGENITAL PULMONARY STENOSIS

Postoperative Observations on Two Hundred and Fourteen Children

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INCREASING interest has been aroused in congenital malformations of the heart accompanied with cyanosis since Blalock and Taussig first reported a surgical technic to relieve congenital pulmonary stenosis.[1] In 1946, Potts, Smith and Gibson[2] described a modified technic for alleviating the symptoms arising from this condition. In either instance an additional artificial channel is created which is physiologically similar to a patent ductus arteriosus. We should like to report on the progress of the first 214 children operated on at Children's Memorial Hospital for congenital pulmonary stenosis. The future course of these patients is a matter of conjecture, and a long range study will be necessary. However, sufficient time has elapsed for us to make some preliminary postoperative observations.

The preoperative diagnosis was tetralogy of Fallot in 199 cases and tricuspid atresia in 15 cases. An aortic-pulmonary anastomosis was established in 177 cases; a Blalock operation was performed in 21 cases, and in 1 case a localized stenosis of the left pulmonary artery was resected. Anastomosis was not performed in 15 cases; atresia of the pulmonary artery prevented anastomosis in 12 of these. One child died before the anastomosis could be completed. It was found impossible to perform a Blalock operation in an older child with a right aortic arch because of an abnormally short subclavian artery. At reoperation the Blalock procedure was performed on the opposite side with success. In another child an anastomosis of the subclavian to the pulmonary artery would have caused severe compression on a huge azygos vein. Each time this vessel was constricted preparatory to attempting the anastomosis, the heart for some unexplained reason promptly stopped beating. Consequently, the procedure was abandoned.

Seven of the 15 children who underwent an exploratory thoracotomy died shortly after surgery. Two patients showed slight improvement in color and exercise tolerance, presumably owing to the freeing of adhesions around a very

From the Children's Memorial Hospital, Chicago.

1. Blalock, A., and Taussig, H. B.: Surgical Treatment of Malformations of Heart in Which There is Pulmonary Stenosis or Pulmonary Artesia, J. A. M. A. **128**:189 (May 19) 1945.

2. Potts, W. J.; Smith, S., and Gibson, S.: Anastomosis of Aorta to Pulmonary Artery: Certain Types in Congenital Heart Disease, J. A. M. A. **132**:627 (Nov. 16) 1946.

tiny pulmonary artery or because of the creation of new vascular channels to the lung by scarification of the visceral pleura and resection of the parietal pleura. The other children showed no change after exploration.

An anastomosis was established in 199 children of this series; 18 died in the immediate postoperative period, and 1 lost his life in an automobile accident. Of the other 180, we have been able to follow 145.

Paroxysmal dyspnea occurred in 66 children prior to surgery and has not been observed in any patient postoperatively. The average preoperative values for red blood cell count and hemoglobin level were 6,930,000 per cubic millimeter and 18.3 Gm. per 100 cc. respectively. The average postoperative values were 5,350,000 per cubic millimeter and 14.4 Gm. per 100 cc.

The decrease in cyanosis following surgery was usually immediate and quite marked (table 1). In one patient (J. W., case 77) the cyanosis was significantly less after surgery, only to become marked in intensity six months after surgery. She died shortly thereafter at her home. The details of her death are not known, and a postmortem examination was not performed, but in view of her course the

TABLE 1.—*Observations on Cyanosis**

Degree of Cyanosis	Preoperative	Immediately Postoperative	6 Months Postoperative	12 Months Postoperative	24 Months Postoperative	36 Months Postoperative
None	0	104	61	44	21	5
Faint	23	43	35	24	13	5
Mild	38	23	7	7	3	1
Moderate	89	5	0	0	1	0
Marked	30	0	1	0	0	0
Not recorded	0	5	6	3	4	0
Total	180	180	110	78	42	11

* Figures refer to number of cases.

possibility must be considered that the anastomosis had closed. In the majority of cases the improvement in cyanosis observed immediately after surgery has remained essentially unchanged throughout the period of observation. In a few instances a continued lessening of the cyanosis has occurred. Frequently when cyanosis has disappeared from the lips, it has still been faintly apparent in the finger nails.

The changes in the clubbing of the fingers and toes have been much slower to appear; however, usually such changes are fairly complete by the end of the first year, but in most cases a suggestion of clubbing persists.

The increase in exercise tolerance has been encouraging in all cases and quite dramatic in a few instances. D. S. (case 1) was 2 years old at the time of surgery and could not stand up alone. Within a few months after operation she was walking and playing with other children, and she is now able to carry on normal activity, except for unusually heavy exercise involving prolonged running. J. E. (case 21) was 6 years old at the time of operation. He was unable to walk more than 25 feet (7.6 meters) before squatting to rest. Fourteen days after surgery he was exercised along the halls of the hospital and was able to walk approximately three fourths of a mile (1.2 kilometers) before getting tired and short of breath.

He has been seen at intervals since then, and three years after surgery he has no limitation of activity, even after severe exercise. In a few similar instances the parents maintain that the children show no cyanosis or dyspnea even on extreme exercise. These cases are the exception rather than the rule, however, and most of the children fall into the category of grade III activity (table 2).

In contrast to the cases with more favorable results are those in which improvement has occurred, but to a lesser degree. R. S. (case 48) was 7½ years old at the time of surgery and could walk only one-half block before squatting to rest. Since then his exercise tolerance has increased so that he can now walk two to three blocks before resting. He no longer squats when short of breath but merely

TABLE 2.—*Observations on Exercise Tolerance**

Degree of Tolerance †	Preoperative	6 Months Postoperative	12 Months Postoperative	24 Months Postoperative	36 Months Postoperative
Grade 0	19	2	0	1	0
Grade I	62	0	0	2	0
Grade II	56	28	19	6	2
Grade III	0	54	44	26	8
Grade IV	0	3	4	3	1
Not recorded ‡	43	23	11	4	0
Total	180	110	78	42	11

* Figures refer to number of cases.
† The criteria used for grading exercise tolerance are grade 0, unable to walk 25 feet; grade I, able to walk 25 feet to less than a block; grade II, able to walk over a block; grade III, mild cyanosis and dyspnea on severe exercise, and grade IV, no unusual fatigue, cyanosis or dyspnea on severe exercise.
‡ These figures include those for children too young to be evaluated accurately.

TABLE 3.—*Observations on Cardiac Enlargement*

	Preoperative (160 Cases)	Immediately Postoperative (115 Cases)	6 Months Postoperative (71 Cases)	12 Months Postoperative (58 Cases)	24 Months Postoperative (23 Cases)	36 Months Postoperative (7 Cases) *
Cardiothoracic ratio	0.55	0.58	0.61	0.59	0.61	0.64
Per cent †	3	13	29	29	41	66

* These figures include data from two of the seven patients described as having severe cardiac enlargement.
† The per cent of enlargement above normal was determined by the long and short diameter method.[3]

sits down. Squatting, like paroxysmal dyspnea, has disappeared after a successful anastomosis.

The heart has enlarged to some degree after surgery in all cases. This has been demonstrable by physical examination or by roentgenography. Although we recognize the fact that measurement of the cardiac silhouette involves many variables, we have included such measurements in order to show the relative enlargement of the heart postoperatively (table 3). Measurements were discarded whenever the diaphragm was unusually high or if the patient was rotated. The preoperative cardiothoracic ratio was higher than the usually accepted normal, as one would expect in the transverse heart of tetralogy of Fallot. On the other hand, there was no significant enlargement when measurement was done by the long and short diameter method.[3]

3. Meyer, Ralph R.: A Method of Measuring Children's Hearts, Radiology **53**:363, 1949.

Only minimal (5 to 10 per cent) cardiac enlargement occurred in seven patients, in spite of excellent improvement in cyanosis and exercise tolerance following surgery (D. S., case 1; R. S., case 57; A. K., case 72; J. B., case 73; P. E., case 107; D. Z., case 186, and M. B., case 189). Most of the children have shown mild (15 to 35 per cent) cardiac enlargement, which has usually occurred within the first six months after surgery.

Seven children have shown severe (85 to 180 per cent) cardiac enlargement with chronic heart failure requiring digitalis therapy (J. P., case 14; R. Y., case 27; T. M., case 64; B. S., case 98; J. H., case 191; D. A., case 200, and V. F., case 212). In each of these cases, unusual cardiac enlargement was apparent within six months after surgery and there was no significant increase after 12 months. The patient with the severest cardiac enlargement (J. P., case 14) was digitalized 11 months after surgery, at which time her heart was 160 per cent enlarged. She has had a clinical pulsus alternans for the past 27 months, and when she was last seen, 36 months after surgery, her heart was 175 per cent enlarged. This 15 year old girl could walk only 100 feet (30.5 meters) prior to surgery and in spite of her postoperative course is now able to attend a school for handicapped children. Four of the other children show symptomatic improvement and decreased cyanosis in spite of marked cardiac enlargement. One patient (J. H., case 191) died 11 months after surgery and four months after digitalis medication was started. D. A. (case 200) was given digitalis therapy four months after surgery and died seven months postoperatively. Postmortem examination revealed similar findings in each case. A tetralogy of Fallot with a mildly (20 per cent) overriding aorta was present; however, there was a ring type valvular stenosis rather than the usual stenosis of the infundibulum of the right ventricle. J. H. also had a moderate-sized interauricular septal defect.

Two other patients in this series have manifested cardiac failure without severe enlargement of the heart. D. P. (case 19) was 2½ years old at the time of surgery and was unable to walk more than one-half block. She showed marked improvement postoperatively in exercise tolerance, but 12 months after surgery her heart was enlarged 55 per cent and cardiac failure was manifested by an enlarged, tender liver and peripheral edema. She was recently seen at a 36 month postoperative visit, at which time she was still taking digitalis and was attending school and her heart showed no significant change in size (45 per cent enlargement). J. A. (case 140) manifested moderate cardiac enlargement two weeks after surgery, with peripheral edema and an enlarged liver. His cardiac failure responded promptly to digitalis therapy, which was maintained for two months. He was seen six months later, at which time there was no evidence of failure and his heart had not increased in size.

Five children in addition to those described above have died during a 3½ year period of observation. M. O. (case 4) and T. R. (case 59) died 2½ and two years postoperatively. The anastomosis never functioned in the case of M. O., and he died 15 days after reoperation on the other side. T. R. became mildly improved after surgery but died suddenly from a ruptured pulmonary artery to the upper lobe of the left lung. Autopsy in both cases revealed transposition of the great vessels in addition to pulmonary stenosis. One child (C. K., case 68) died three

months after surgery, and a brain abcess in addition to tetralogy of Fallott was demonstrated. N. D. (case 133) died three months after operation, but no details are available. R. E. (case 201) died seven months postoperatively at another hospital as a result of acute cardiac failure following a bilateral herniorrhaphy.

COMMENT

The two children in this series who died after surgery and who had transposition of the great vessels with pulmonary stenosis merit additional consideration. The children both had moderate exercise intolerance, squatted when short of breath and had a fair boot-shaped heart with a fair shelf and a good pulmonary window. In retrospect, the only discrepancy in the diagnosis of tetralogy of Fallot was to be found in the electrocardiogram. In both cases, the QRS complex was deeply inverted in lead I and a Wilson phenomenon [4] was present in the chest leads; however, the QRS in lead III was of very low amplitude or actually slightly inverted. In our opinion the diagnosis in a case that otherwise seems to be one of tetralogy of Fallot should be seriously questioned if the QRS in lead III is not tall and upright.

That the Blalock or Potts-Smith procedure alleviates the symptoms occurring in certain types of congenital pulmonary stenosis is well demonstrated in this series. The degree of response has varied in individual cases, and so far we have been unable to predict with any degree of surety which patients will receive the greatest benefit from surgery. In cases in which there is an atresia of the main pulmonary and proximal left pulmonary arteries, an anastomosis to the distal portion of the left pulmonary artery will not give as good a result as when there is no atresia, merely because the additional blood is sent only to the left lung. However, in all cases in which a satisfactory anastomosis has been created there has been gratifying improvement.

Postoperative cardiac enlargement is to be expected if the anastomosis remains patent. In the first 42 cases of this series the incision in the aorta and pulmonary artery was 8 mm. in length. In the other cases the incision has usually been 6.25 mm. long. An opening much smaller in size is not very practical because of the danger of thrombosis at the site of the anastomosis, with resultant closure. In spite of this attempt to reduce the size of the anastomotic channel, there has been no significant reduction in the incidence of cardiac failure or severe cardiac enlargement.

The future course of these children who have been operated on is difficult to predict. We are now seeing significant and rather consistent electrocardiographic changes two to three years after surgery. The P waves are much less peaked and tall than they were before surgery, and evidence of right heart strain has commonly disappeared. The QRS in lead I is diphasic rather than being deeply inverted, and the Wilson phenomenon in the chest leads has disappeared. It is difficult to see how this type of surgery could possibly remove the existing strain on the right ventricle, but better oxygen saturation in the coronary circulation undoubtedly occurs. The changes in the QRS complex may represent the beginning of left heart preponderance, which would be compatible with the changes in physiology resulting from the surgical procedure.

4. The Wilson phenomenon or Wilson block is a retardation of the spread of excitation over the right ventricle. The S wave is broadened and returns in a stepwise manner to the S-T level.

Proper postoperative evaluation of these patients will require at least another 10 to 15 or more years. However, the immediate relief of symptoms, with a change from a life of invalidism to one of relative normalcy, would seem to justify the procedure.

SUMMARY

The first 214 cases in which a Blalock or Potts-Smith procedure was attempted at Children's Memorial Hospital are reviewed. An anastomosis was possible in 199 patients. Eighteen children (9 per cent) died in the immediate postoperative period; 1 child died in an automobile accident three months after operation, and 35 children have not been seen since surgery.

The remaining 145 patients have been observed for postoperative periods ranging from six to 42 months. Eight of these children (5.5 per cent) have died from various causes during the period of observation. The degree of improvement in the surviving children, as shown by changes in cyanosis and exercise tolerance, as well as the degree of cardiac enlargement, is described.

Dr. Harvey White, roentgenologist, evaluated the roentgenograms included in this study.

CARE, FEEDING AND FATE OF PREMATURE AND FULL TERM INFANTS BORN OF TUBERCULOUS MOTHERS

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AT THE end of the last century it was generally accepted that the newborn infant of a tuberculous mother was doomed to inherit the malady. However, by the first quarter of the present century a changing attitude became apparent, largely due to the investigations of French clinicians. In a series of papers Debré and LeLong [1] in 1925 described their procedures, clinical observations and experimental findings.

The newborn were separated from their mothers at birth and were protected from postnatal contacts over a prolonged period. Those that died (15 per cent of the series) were autopsied. Two hundred guinea pigs were inoculated with fragments of viscera (particularly the liver, spleen, mesenteric nodes, bone marrow) to determine the presence of tubercle bacilli, and the findings were negative.

From their studies these authors concluded that death in the early months did not result from hereditary and constitutional factors but rather from artificial feeding and privation of maternal care. They cited the work of Couvelaire and Forssner, who noted a 38 and a 12 per cent mortality, respectively, in infants separated from their tuberculous mothers at birth. Debré and LeLong speculated that with perfection of the technics of artificial feeding and infant care such deaths would be progressively reduced.

That there are undoubted cases of intrauterine infection is accepted, but such cases are rare. They usually occur in instances of overwhelming infection of the mother.[2] On even rarer occasions transplacental infection has been reported when the disease was not marked in the mother.[3]

Drs. Rostler and Salgado were former residents in the Pediatric Division of Sea View Hospital.

From the Pediatric Division, Sea View Hospital for Tuberculosis, and the Pediatric Department, New York Medical College, Flower and Fifth Avenue Hospitals.

1. Debré, R., and LeLong, M.: Different Aspects of Heredity of Tuberculosis: I. Intrauterine Contamination, Ann. méd. **17**:209, 1925; II. Heredity of Tuberculosis, ibid. **17**:601, 1925; III. Mortality Among Children of Tuberculous Parents, Isolated Before Contamination, ibid. **18**:256, 1925; IV. The Infant Born of Tuberculous Parents Separated Before Contamination: Its Growth and Resistance to Disease, ibid. **18**:347, 1925.

2. Siegel, M.: Pathological Findings and Pathogenesis of Congenital Tuberculosis, Am. Rev. Tuberc. **29**:297, 1934. Hughesdon, M. R.: Congenital Tuberculosis, Arch. Dis. Childhood **21**:121, 1946.

3. Grulee, C. G., and Harms, F.: Tuberculosis as a Disease of the Newborn, Am. J. Dis. Child. **9**:322 (April) 1915.

Recently Waissmann,[4] of Argentina, reported that 11 infants died of congenital tuberculosis of a total of 737 delivered of tuberculous mothers, or 1.46 per cent. In a total of 260 infants born at Sea View Hospital over a period of 12 years (1933 to 1945), we did not encounter a single case of congenital tuberculosis. If Waissmann's observations held for our population, we should have had two or three cases.

With present improved methods for feeding and care, the newborn infants of tuberculous mothers should thrive as well as those born of healthy mothers. We believe our data with present day artificial feeding and care fully justify the prediction made by Debré and LeLong.

MATERIAL AND METHODS

For administrative reasons beyond our control the obstetric service unfortunately had to be discontinued in 1945. The data presented relate particularly to the care and feeding of 55 infants born between 1943 and 1945. Certain comparative and correlative data have been culled from the hospital records covering the period as far back as 1933.

The pediatric division of Sea View Hospital is housed in a large modern building with a capacity of 300 beds. It is separated from the other hospital divisions. A nursery is provided for the newborn, in which 10 babies can be cared for. There are three shifts of nurses. The nursery is isolated from the rest of the pediatric division. All sanitary precautions are strictly observed by physicians and nurses. Visitors are never allowed inside the nursery.

After proper identification and other routine obstetric measures are completed, the infant, properly warmed and protected, is immediately transferred by ambulance from the delivery room in the obstetric division to the children's admitting room and thence to the nursery. When the call is received announcing a new admission, a bassinet is prepared, with the usual precautions. Provision is made for weighing and examination by the physician in charge. Babies weighing 5½ pounds (2,500 Gm.) or under are treated as premature, with all the necessary precautions and special measures. The incubator used is manufactured by Morgenthaler, model 150. An oxygen tank is always at hand in close proximity to the infant, and oxygen is administered by the open funnel method when needed. Clyses of sodium chloride and Hartmann's solutions (containing sodium chloride, sodium lactate, calcium and potassium phosphates) are administered when necessary.

For the first 12 hours nothing is given by mouth, and then 10 per cent dextrose or saline solution is given orally in the next 12 hours prior to the introduction of the formula.

STANDARDIZATION OF THE FORMULA FOR FULL TERM NEWBORN INFANTS

We were moved by the following considerations in the selection of the ingredients for a formula which we believed was sound and would meet not only the optimum needs of the high percentage of premature infants we encountered but also those of the full term newborn infants.

General Considerations.—1. The protein requirement was estimated as a little less than the pounds of body weight in ounces of evaporated milk. Thus, a 7 pound (3,175 Gm.) baby would start with a total of 6 ounces (177 cc.) of evaporated milk for 24 hours. Feedings were given six times and later five times a day.

2. Total fluid needs were calculated on the basis of a little less than three times the pounds of body weight in ounces. For a 7 pound infant the initial total fluid requirement for 24 hours was judged to be 18 to 21 ounces (532 to 621 cc.).

4. Waissmann, M.: Tuberculosis congénita, Thesis for the Doctorate, Buenos Aires, Imprenta de Alfredo Frascoli, 1942.

3. The carbohydrate content was computed on the basis of one-third the caloric need.

4. About 45 calories per pound (454 Gm.) of body weight was estimated as the base line in the energy quotient for full term infants.

5. Vitamins were added as required. Since vitamin C is reduced in milk and absent in evaporated milk, 50 to 100 mg. of ascorbic acid was added to the formula from the start. Vitamins A and D were added as percomorph liver oil [5] as soon as expedient.

Type of Nutrients.—Evaporated milk was used exclusively for the following reasons:

1. It is a homogenized product. In the process of digestion a soft curd is produced that closely resembles breast milk curd. It is a uniformly better product than any other form of soft curd milk.

2. The homogenization process breaks up the fat globules into a smaller size than that of those present in other forms of cow's milk, and evaporated milk, therefore, more nearly resembles breast milk in this respect also.

3. Because of the small particle size of the protein elements a greater surface of the protein molecules is exposed to enzyme digestion. The coefficient of digestibility is, therefore, higher for this form of milk than for any other.

4. The heat process to which evaporated milk is subjected coagulates the albumin and globulin fractions and thereby reduces its allergenicity.[6] This relative denaturation is more effectively achieved in evaporated milk than in ordinary boiled milk or other heated proprietary milks. The heat treatment also effectively denatures any foreign allergens that may be present in the raw milk as a result of the cow's food.

5. Evaporated milk more nearly resembles human breast milk than any other milk. For our purposes it was considered superior to the latter because of the uniformity of its protein and fat ingredients, its higher calcium, phosphorus and nitrogen content,[7] its denaturation, uniform digestibility, the absence of foreign substances and its sterility.

Maltose and dextrins (dextri-maltose[8]) were the sugars chosen because (1) they are more slowly fermented in the intestinal tract; (2) they are free of allergenicity [8]; (3) they are less sweet and, therefore, create fewer psychically based feeding difficulties, and (4) the preparation used contains a higher percentage of natural vitamin B (thiamine).[9]

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5. The percomorph liver oil used provided 1,250 units of vitamin A and 180 units of vitamin D per drop.

6. Ratner, B., and Gruehl, H. L.: Anaphylactogenic Properties of Milk: Immunochemistry of Purified Proteins and Antigenic Changes Resulting from Heat and Acidification, Am. J. Dis. Child. **49**:287 (Feb.) 1935. Ratner, B.: The Treatment of Milk Allergy and Its Basic Principles, J. A. M. A. **105**:934 (Sept. 21) 1935.

7. (*a*) Benjamin, H. R.; Gordon, H. H., and Marples, E.: Calcium and Phosphorus Requirements of Premature Infants, Am. J. Dis. Child. **65**:412 (March) 1943. (*b*) Gordon, H. H.; Levine, S. Z., and McNamara, H.: Feeding of Premature Infants, ibid. **73**:442 (April) 1947.

8. Ratner, B., and Gruehl, H. L.: Anaphylactogenic Properties of Malted Sugars and Corn Syrup, Am. J. Dis. Child. **49**:307 (Feb.) 1935.

9. Richter, C. P.: Nutritive Value of Dextri-Maltose Determined by the Single-Food Choice Method, Proc. Soc. Exper. Biol. & Med. **59**:260, 1945.

Calcium caseinate (casec®) was chosen to enrich the formula because additional protein concentration can be achieved without increasing the volume of the formula. Smaller newborn and particularly premature infants require more protein than do large and full term babies.[10]

Ascorbic acid was added for the reason that it aids in the intermediary amino acid metabolism, particularly of premature infants.[11]

SPECIAL CONSIDERATIONS FOR PREMATURE INFANTS

The type of formula used for the premature infants was the same as that described for the full term newborn. It was theoretically calculated on the basis of the weight of the premature infant. Thus, if the infant weighed 4 pounds (1,814 Gm.), the ingredients were 3 ounces (89 cc.) of evaporated milk, 9 ounces (266 cc.) of water, about 2 tablespoons (30 cc.) of dextri-maltose® and 50 to 100 mg. of ascorbic acid. As the infant thrived, ½ to 1 tablespoon (7.5 to 15 cc.) of calcium caseinate was added. This formula was estimated to give about 60 calories per pound, or 110 to 125 calories per kilogram of body weight.

However, caution was exercised not to force on the premature infant any more than he could take. To the very small premature infant, the formula was administered in ½ or 1 teaspoon (2 or 5 cc.) doses by dropper, given 12 times a day or oftener. Thus, a premature infant would start with about 20 calories per pound of body weight, and that amount was given until he was capable of digesting more. The increases in formula were made cautiously. No attempt was made to accelerate the infant's gain. The total formula was not changed until the baby took the total amount. With the small premature infants less than three times the body weight in ounces was given in order to concentrate the food. Clyses of 10 to 20 cc. were given subcutaneously to those that appeared dehydrated. At no time was any specific rule of thumb followed. The quantity of the formula and the fluid administrations were determined daily for each infant. When 1 ounce (30 cc.) of formula or more per feeding was taken, the feedings were reduced from 12 to eight a day. When the premature infant was able to take 2 ounces (59 cc.) or more, the number of feedings a day was reduced to six. As soon as the baby was thriving visibly and could take amounts of formula adequate to give him three times the body weight in the 24 hour period, the feedings were reduced to five a day.

At times and for short intervals the volume of fluid was increased beyond three times the body weight when the infant required it and then returned to the normal amount as soon as possible. The fluid quantity, therefore, varied with the requirement of the infant as judged by his desire and ability to take it.

Oxygen was administered when the infant showed any evidence of cyanosis or in any way appeared to need stimulation.

Percomorph liver oil was added as soon as it was found expedient digestively. This was given in drop doses gradually increased from 2 to 3 to 10 to 15 drops per day.

For an example of a typical feeding schedule for a premature infant, see table 1.

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10. Gordon, H. H., and Levine, S. Z.: Metabolic Basis for Individualized Feeding of Infants, Premature and Full Term, J. Pediat. **25**:464, 1944.

11. Levine, S. Z.; Marples, E., and Gordon, H. H.: A Defect in the Metabolism of Aromatic Amino Acids in Premature Infants: The Role of Vitamin C, Science **90**:620, 1939.

TABLE 1.—*Example of Feeding Schedule of a Premature Infant*

Date	Age, Days	Weight		Feedings		Formula				Vitamins	Other Foods
		Lb.	Oz.	Amount	No.	Evaporated Milk, Oz.	Water, Oz.	Dextri-Maltose,* Tablespoons	Calcium Caseinate, Tablespoons		
2/ 8/44	1	2	14	4 cc.	12	2	4	1	..	50 mg. ascorbic acid	.....
2/17/44	10	2	6½	8 cc.	12	2	4	2	..	50 mg. ascorbic acid	.....
2/18/44	11	2	7	10 cc.	12	2	4	2	..	50 mg. ascorbic acid	.....
2/21/44	14	..	..	14 cc.	12	3	6	3	..	50 mg. ascorbic acid	.....
2/28/44	21	2	15	16 cc.	12	3	6	3	..	50 mg. ascorbic acid	.....
3/ 1/44	22	3	½	18 cc.	12	3	6	3	..	50 mg. ascorbic acid	.....
3/ 3/44	24	3	4	20 cc.	12	3	6	3	..	50 mg. ascorbic acid	.....
3/ 5/44	26	..	..	22 cc.	12	3	6	3	..	50 mg. ascorbic acid	.....
3/10/44	31	3	15	36 cc.	8	4	8	4	¼	50 mg. ascorbic acid; 5 drops percomorph liver oil	.....
3/13/44	34	4	3	40 cc.	8	4	8	4	½	50 mg. ascorbic acid; 5 drops percomorph liver oil	.....
3/21/44	42	4	14	42 cc.	8	4	8	4	½	50 mg. ascorbic acid; 5 drops percomorph liver oil	.....
3/25/44	46	5	2	2¼ oz.	6	4	13½	3	1	50 mg. ascorbic acid; 5 drops percomorph liver oil	.....
4/14/44	66	6	2	3 oz.	6	5	13	4	1	Orange juice * worked up to 1 oz.	.....
5/ 1/44	83	7	4	4 oz.	6	6½	17½	5	1	Orange juice worked up to 1 oz.	.....
5/16/44	98	8	2	5 oz.	6	7½	22½	5	1½	Orange juice worked up to 1 oz.	.....
5/26/44	108	8	14	6 oz.	5	8	22	4	1½	Orange juice worked up to 1 oz.	Pablum ●; pabena ●; egg yolk

* Use of ascorbic acid was discontinued.

ANALYSIS OF RESULTS OBTAINED WITH FIFTY-FIVE INFANTS CARED FOR UNDER THE REGIMEN OUTLINED

From the data recorded in table 2 it will be noted that 44 per cent of the infants delivered in this series were premature, weighing at birth 5½ pounds or under, the average weight for the premature infants being 4.2 pounds (1,905 Gm.). For the full term infants the average weight was 7 pounds. The over-all average weight for the 55 infants was 5.6 pounds (2,540 Gm.), which is in accord with the general observation that infants born of tuberculous mothers are usually smaller.

TABLE 2.—*Incidence and Gain in Weight During Hospital Stay of Fifty-Five Infants of Tuberculous Mothers (1943 to 1945)*

	Weight		Sex		Race		
	Premature	Full term	Female	Male	White	Negro	Comment
Number and percentages	24 44	31 56	28 51	27 49	25 45	30 55	.....
Mean birth weight, lb.	4.2	7	5.4	5.8	6.1	5.1	Mean weight of premature and full term infants, 5.6 lb.
Mean initial weight loss, oz.	5.2	7	6	7	8.4	5.6	.....
Average gain per day, oz.	0.77	0.84	0.75	0.84	0.77	0.86	.....
Average no. of days in nursery	118 (4 mo.)	97 (3 mo.)	76 (2½ mo.)	123 (4 mo.)	94 (3 mo.)	103 (3 mo.)	.....
Average discharge weight, lb.	10.7	12	12.1	13.3	11.3	11.8	.....

TABLE 3.—*Comparison of Survival Rate Ten Years Ago (1933 to 1935) and Under Present Regimen (1943 to 1945)*

				Survival		
	Total	Death in 1st 24 Hr.	Death After 24 Hr.	After 1st Day, %	Including 1st Day, %	Comment
1933 to 1935	39	2 (5%)	7 (18%)	82	77	Total prematurity, 26% Average age of dead infants, 26 days 5 of 7 who died were premature
1943 to 1945	55	4 (7%)	0	100*	93	Total prematurity, 44% Average age of dead infants, 1 day All who died were premature

* One hundred per cent survival was achieved in this small series. This figure would not prevail in a larger series but is indicative of the high survival rate achieved.

Some, at least of the heavier premature infants, judged solely by the criterion of weight, might in fact be smaller full term infants if the factor of smallness is inherent in the offspring of tuberculous mothers.

The infants were kept in the nursery for an average period of four months for the premature and three months for the full term infants.

Despite the handicap of prematurity that characterized so large a proportion of the infants, it will be noted (table 2) that the infants thrived. The initial loss in weight was within normal range, and the gains in weight were entirely satisfactory. Our figures compare favorably with the expected progress noted among infants born of normal mothers.

Since 100 per cent of our series survived, exclusive of those premature infants who died in the first 24 hours (table 3), it is obvious that the standard formula employed and the care given these infants were highly satisfactory. The figure achieved here, 100 per cent, must be regarded as fortuitous, for deaths might have occurred from causes not related to feeding, as is evidenced in three deaths referred to in table 4. In 1938 a death occurred that was due to aspiration pneumonia,

TABLE 4.—*Analysis of Twenty-Two Deaths in 260 Cases (1933 to 1945)*

	Infant							Mother		
Year	Case	Race	Sex	Age at Death, Days	Birth Weight, Lb.	Oz.	Term	Autopsy Observations	Age, Yr.	Type of Tuberculosis	Death After Birth, Days
1933	1	N	F	27	5	1	Premature	Prematurity; bronchopneumonia	22	Chronic	Alive
1933	2	W	M	51	4	12	Premature	Prematurity; bronchopneumonia	27	Advanced	12
1933	3	W	M	1	2	5	Premature	Prematurity *	26	Advanced	Next day
1933	4	N	M	12	4	15	Premature	Prematurity *	29	Advanced	24
1933	5	N	M	41	2	12	Premature	Prematurity; bronchopneumonia	23	Advanced	55
1934	6	N	M	12	6	12	Full	Bronchopneumonia	18	Chronic	Alive
1934	7	W	F	16	8	10	Full	Bronchopneumonia, hydronephrosis; otitis media	23	Arrested	Alive
1934	8	W	M	27	3	10	Premature	Prematurity	26	Advanced	30
1935	9	W	M	1	1	14	Premature	Prematurity	26	Chronic	Alive
1936	10	N	F	22	5	2	Premature	Congenital heart malformation; prematurity; bronchopneumonia	34	Advanced	Next day
1938	11	W	M	54	5	12	Full	Aspiration pneumonia	23	Advanced	52
1938	12	W	F	85	4	8	Premature	Prematurity; bronchopneumonia	25	Arrested	Alive
1939	13	W	F	1	6	4	Full	Cerebral hematoma	28	Chronic	Alive
1940	14	W	F	1	7	4	Full	Congenital heart malformation	36	Chronic	Alive
1941	15	N	F	1	No weight		Premature	Prematurity	21	Chronic	Alive
1941	16	N	F	105	5	1	Premature	Diarrhea; dehydration toxemia	25	Chronic	Alive
1941	17	N	M	1	1	4	Premature	Prematurity	18	Chronic	75
1942	18	W	M	11	3	14	Premature	Prematurity	17	Advanced	135
1943	19	N	M	1	2	10†	Premature	Prematurity	39	Advanced	18
1943	20	N	F	1	2	11†	Premature	Prematurity; asphyxia	23	Chronic	Alive
1944	21	W	F	1	3	1 †	Premature	Atelectasis of all lobes; prematurity	27	Chronic	Alive
1944	22	N	M	1	3	4 †	Premature	Prematurity	28	Chronic	Same day

* Farber and Potter contend that prematurity is not an acceptable cause of death (New York State J. Med. 41: 2047, 1941).

† The weight in grams is as follows: case 19, 1,191; case 20, 1,219; case 21, 1,389, and case 22, 1,424.

in 1939 one from cerebral hemorrhage and in 1940 one from congenital heart disease. These three deaths occurred in full term newborn infants. The figure of 100 per cent in our series, though fortuitous, does indicate, however, the high degree of survival that can be achieved with the regimen instituted.

It will be recalled that a mortality rate ranging from 12 to 38 per cent was recorded up to 1925.[1] In table 3 it will be noted further that there was an 18 per cent mortality, particularly among the premature infants, in the three year period (1933 to 1935) ten years prior to institution of our regimen. It seems reasonable to assume that the deaths were attributable to the feeding and care of the infants. In table 5 is recorded the fate of 11 babies of our present series, nine of whom were premature and born of mothers with advanced tuberculosis who died shortly after the birth of their infants. Not a single infant died who survived

the first 24 hours. The only death in the first 24 hours was that of an infant weighing 1,191 Gm. This record also may be fortuitous, but, nevertheless, it emphasizes signally the better survival rate of the present series than of the infants surveyed over the prior 10 year period (see table 3 for details) and recorded in the literature previous to 1925.

ANALYSIS OF DEATHS

In the present series (1943 to 1945) there were four deaths, which all occurred in the first 24 hours (table 3). These were all of small premature infants, weighing 1,191, 1,219, 1,389 and 1,474 Gm., respectively (table 4). At necropsy none

TABLE 5.—*Fate of Infants Born of Mothers Who Died of Advanced Tuberculosis Shortly After Delivery*

	Mother				Infant						
							Weight		Days	Discharge Weight	
Patient	Race	Age, Yr.	Type of Tuberculosis	Death After Birth	Sex	Term	Lb.	Oz.	in Nursery	Lb.	Oz.	Comment
G. G.	W	37	Advanced	1½ mo.	M	Premature	4	8	113	9	0	Mantoux reaction negative
L. R.	N	21	Advanced	3 mo.	F	Premature	4	7	157	12	3	Mantoux reaction negative
A. G.	W	39	Advanced	19 days	F	Premature	2	10	0	0	0	Died 1st day
B. T.	N	19	Chronic	11 days	F	Premature	3	0	100	7	4	Mantoux reaction negative
A. B.	N	26	Advanced	2½ mo.	M	Premature	5	3	177	16	0	Inguinal hernia; Mantoux reaction negative
D. C.	W	24	Advanced	29 days	M	Premature	4	15	327	18	2	Atelectasis of right upper lobe at birth; otitis media; inspiratory stridor; Mantoux reaction negative
D. G.	N	23	Advanced	1½ mo.	M	Full	6	6	99	12	10	Mantoux reaction negative
A. H.	N	24	Advanced	27 days	M	Premature	5	5	81	9	12	Purulent conjunctivitis and diarrhea which cleared
P. R.	N	19	Advanced	1½ mo.	M	Full	5	15	49	8	3	Mantoux reaction negative
C. H.	N	26	Advanced	24 days	M	Premature	4	2	154	11	14	Mantoux reaction negative
A. F.	W	33	Advanced	14 days	F	Premature	4	7	114	8	12	Mantoux reaction negative

showed evidence of tuberculosis. No deaths occurred in 1945. However, in the preceding period 10 years earlier (1933 to 1935) there were nine deaths. Two infants died in the first 24 hours, but the remaining seven died 12 to 51 days after birth, largely from bronchopneumonia and prematurity, suggesting that the resistance of the present series may have been enhanced by the feeding and care instituted.

RELATION OF PREMATURITY TO TUBERCULOSIS

That chronic infection of the mother increases the incidence of prematurity is well known. If the general incidence of prematurity is 7 to 11 per cent,[12] then our figure of 23 per cent for the period between 1933 and 1945 is high (table 6).

12. Dunham, E. C.: Premature Infants: A Manual for Physicians, Bulletin 325, Federal Security Agency, United States Children's Bureau, 1948.

That we obtained a 44 per cent incidence in our present series, 1943 to 1945, may be due to the meagerness of the sample studied. The fact remains that it is the consensus that the incidence of prematurity is exceedingly high in the offspring of tuberculous mothers.

What is of greater interest perhaps is the observation (table 6) that the mothers with arrested or chronic tuberculosis have an incidence of 22 per cent premature deliveries, whereas with the mothers who had advanced tuberculosis and died soon after delivery the incidence of prematurity rose to the high figure of 64 per cent, the figure in the present series being proportionately higher. It is fair to assume, therefore, that prematurity is related to the severity of the disease in the mother.

Despite this high incidence of prematurity in the offspring of the mothers who died of advanced tuberculosis, it is equally astonishing to observe (table 5) that all but one of the premature offspring survived who were born of the 11 mothers that died of advanced tuberculosis shortly after delivery. The one premature infant who died weighed 1,191 Gm. and died in the first 24 hours after birth.

TABLE 6.—*Influence of Severity of Tuberculosis of the Mother on Incidence of Prematurity in 260 Cases (1933 to 1945)*

	Total Number	Full Term Infants	Premature Infants	Percentage of Prematurity
Total cases, 1933 to 1945	260	201	59	23
Mothers with chronic or arrested tuberculosis who lived	221	171	50	22
Mothers who died from tuberculosis shortly after delivery	39*	14	25	64
Present series, 1943 to 1945	55	31	24	44
Mothers who lived	44	29	15	34
Mothers who died	11	2	9	81

* Mortality of the mothers was 17.6 per cent.

PROGRESS

It was not possible to follow up all our patients. We succeeded in about a third of the cases for about two years.

One of the premature infants, weighing 1,219 Gm., who died in the first 24 hours was one of twins. The surviving twin, who weighed 1,248 Gm. at birth, remained in the nursery for about four months and was discharged weighing 12½ pounds (5,700 Gm.). The twin who died was shown at necropsy to have congenital heart disease but no evidence of tuberculosis.

The children on whom we were able to secure progress reports presented an entirely satisfactory picture, showing a good gain in weight and normal development, negative Mantoux reaction and negative findings on roentgenograms at 2 years of age.

It may be of interest to describe one of the cases, that of an infant who weighed 8 pounds (3,629 Gm.) at birth and who at 2 years of age weighed 29 pounds (13.2 Kg.) and was 33½ inches (85 cm.) in height. This child was sent home to his mother when he was 41 days old. The mother was later sent to the Otisville Municipal Sanatorium and subsequently transferred back to Sea View Hospital. A male cousin of the mother, who himself later died of tuberculosis at Sea View Hospital, had stayed with the family off and on. On the occasion of these visits he was wont to spend the night there. The mother states that this cousin never kissed the baby, but she admitted that she herself had. Although the child had a positive Mantoux reaction at

2 years of age, his roentgenograms showed only a hilar lymphadenopathy suggestive of a receding primary pulmonary lesion.

Another infant at the age of 14 months weighed 22 pounds (9,980 Gm.) and was admitted to Harlem Hospital with otitis media and lobar pneumonia. The Mantoux reaction was negative, and the child made an uneventful recovery.

It would have been instructive to have a follow-up report on each of the infants, but we feel quite certain that if any of them had acquired tuberculosis he would undoubtedly have been returned to Bellevue or some other city hospital and a record requested from us. We received no such requests on the infants for whom we had no follow-up records.

Despite this incomplete evidence, it does not seem unreasonable to infer that an infant born of a tuberculous mother who survives the early period and does not become infected with tuberculosis through contact remains signally free of tuberculosis and thrives as does any infant born of a normal mother.

COMMENT

The usual reasons given for the insistence on breast milk feeding, especially from the somatic standpoint, are (1) ease of digestion, (2) relative ease of diet regulation, (3) low bacterial content, (4) relative freedom from infection and digestive disturbances and (5) good growth.

These criteria, we believe, are adequately satisfied by the formula we used, as is evidenced by the record of our series of patients.

Breast milk has certain deficiencies not present in the evaporated milk formula. For example, breast milk is low in protein content. A premature or immature infant often cannot thrive maximally on the limited protein quota of human milk.[13] Added vitamins must be supplied in both types of feeding, but breast milk does have a greater deficiency than cow's milk.[14] An important recent contribution is the demonstration that calcium utilization by the premature baby may be subnormal on a diet of human milk. The retention of calcium is improved and becomes optimal when cow's milk is the source of calcium and phosphorus. These minerals are indispensable for normal growth of the skeletal system and other tissues.[7a]

Gordon, Levine and McNamara [7b] expressed the opinion that evaporated milk and skim milk are superior to human milk for premature infants. Striking evidence for the value of evaporated milk in the feeding of premature infants is presented by Gruber and his associates [15] who reported on a large series, 992 premature infants, fed a mixture of evaporated milk and dextri-maltose.* Their mortality was 13.5 per cent. Their figures included deaths in the first 48 hours, which comprised three fourths of all the deaths. When one realizes that close to 50 per cent of all neonatal deaths occur among premature infants, this experience is truly impressive. It offers supportive evidence for the findings in our present study. Our experience is in agreement with that of Gruber and his associates, who stated that this mixture should be recommended for general use in the case of the premature infant and, one might safely add, for the full term baby.

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13. Gordon and others.[7b] Gordon and Levine.[10]

14. Knott, E. M.; Kleiger, S. C., and Schultz, F. W.: Is Breast Milk Adequate in Meeting the Thiamine Requirement of Infants? J. Pediat. **22**:43, 1943.

15. Gruber, S.; Litvak, A.; Rascoff, H., and Norton, R.: The Hospital Progress of 992 Premature Infants Fed Evaporated Milk Carbohydrate Mixtures, J. Pediat. **35**:70, 1949.

It is generally stated that about 3 or 4 per cent of all premature births result from the presence of tuberculosis in the mother. This must not be confused with our figure of an incidence of 23 per cent premature births among 260 deliveries over a period of 12 years, and 44 per cent of the 55 cases reported on from 1943 to 1945 at Sea View Hospital. The first figure, 3 to 4 per cent, is based on the incidence in the birth rate as a whole and would seem to indicate that a small number of tuberculous women have children. Our figures, 23 and 44 per cent, are based on the incidence in a selected group and would seem to indicate that the incidence of prematurity is high in the offspring of tuberculous mothers (table 6).

The splendid results we obtained in the reduction of the mortality rate among the newborn of tuberculous mothers, compared with the record of the past decades, can be credited to the use of the standardized mixture of evaporated milk and dextri-maltose,* the administration of supplementary vitamins and the generally improved care.

However, we must note that the death rate in the first day has not changed. It has been emphasized [16] that it is not so generally realized that the mortality of the first day of life has shown practically no decrease in the last 25 years. These deaths constitute about one third of all deaths during the first year of life. Tyson [17] was in large part justified in his criticism that the continued high mortality during the first 24 hours of life indicates that the medical care is inadequate at this time. In many cases, however, death is due to factors existing before birth, and as a consequence postnatal care, no matter how adequate, fails.

Immediate separation of the newborn from the tuberculous mother is essential, and our study fully corroborates the conclusions of Debré and LeLong [1] in 1925 and of Duthoit and Dubois [18] in 1936. These investigators found that the disease did not develop in any of the infants who were removed from contact with their tuberculous parents, whereas among those who remained in a contaminated environment there was an appreciable morbidity, as well as mortality, from tuberculosis even though careful precautions were taken. The one case in our series in which tuberculosis developed through environmental contact nicely demonstrates this point.

Our experiences with respect to the birth weight and subsequent gain are also in accord with those of Debré and LeLong and, more recently, Urquijo and Waissmann.[19] The birth weight of the infant born of a mother with moderate tuberculosis does not differ from that of the healthy nontuberculous infant born of a healthy mother (table 2).

Although advanced tuberculosis of the mother is regarded as the cause of prematurity, it is not due to the tuberculous infection but to the generally disturbed metabolism of the mother. Urquijo and Waissmann demonstrated this in a large series of cases. We believe that the fact that only two full term infants in our

16. Duffield, T. J.; Parker, S. L., and Baumgartner, L.: Birth Weight and Its Relation to Neonatal Mortality, Child **5**:123, 1940.

17. Tyson, R. M.: Immediate Care of the Newborn in Relation to Neonatal Mortality, J. A. M. A. **124**:351 (Feb. 5) 1944.

18. Duthoit, R., and Dubois, R.: Development During Early Life of Children Born of Tuberculous Parents, Bull. Soc. Pédiat. de Paris **34**:708, 1936.

19. Urquijo, C. A., and Waissmann, M.: Study of Birth Weights and Ponderal Growth of Children of Tuberculous Mothers, J. Pediat. **21**:787, 1942.

present series, 1943 to 1945, were born to 11 mothers who died of advanced tuberculosis is significant evidence that the severity of the maternal tuberculosis is related to prematurity (table 5). In table 6 the comparison between severe and moderate tuberculosis of the mother in relation to prematurity is further amplified. In the mothers who had moderate or arrested tuberculosis (over the 12 year period, 1933 to 1945) there was a 22 per cent incidence of prematurity, whereas in the advanced cases the incidence was 64 per cent. In like manner during the period 1943 to 1945, when the incidence of prematurity was 34 per cent among mothers with the moderate disease, it rose to 81 per cent among those with the advanced disease.

The gain in weight of the infant born of a tuberculous mother with a normal weight is similar to that of the infant born of a healthy mother. The gain in weight of the infant weighing less than 2,500 Gm. born of a tuberculous mother is similar in our series to that of the infant of equivalent weight born of a nontuberculous mother (table 2). Inasmuch as it is frequently stated that this obtains but in less degree for the premature infant, we feel that our record must be attributed to the improved feeding and care.

CONCLUSIONS

The incidence of prematurity is exceedingly high in the offspring of tuberculous mothers, ranging from 23 to 64 per cent, depending on the severity of the disease in the mother.

The prematurity is related to the severity of the disease in the mother not because of the tuberculous infection but because of the impoverished nutritional status of the mother.

In an infant immediately removed from contact with the tuberculous mother, who continues to remain in an environment free of tuberculosis, the disease does not develop.

Although congenital tuberculosis does undoubtedly occur, we did not encounter a single case of transplacental tuberculosis in our series of 260 births, even though 17.6 per cent of the mothers died of advanced tuberculosis shortly after delivery.

A standard diet of evaporated milk and dextri-maltose,® with the supplementation of ascorbic acid, percomorph liver oil and calcium caseinate given the premature, as well as the full term, infants born of tuberculous mothers resulted in a growth pattern and development comparable to that observed in premature and full term infants born of healthy mothers.

IMMUNIZATION IN THE YOUNG INFANT

Response to Combined Vaccines: I-IV

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I. INTRODUCTION

THE ABILITY of young infants to produce antibodies had not until recently been explored. The examination of some of the factors related to this problem is the object of this study.

The thesis of Hirszfeld and the related studies of many others reported during the first 25 years of this century were ably summarized by Baumgartner [1] in 1934. She concluded that the evidence presented indicated the development in the person during early life of a certain biochemical reflex of antibody production, a development comparable, for example, to that of sexual maturity. This expressed the common belief of that time that infants were incapable of forming antibody, and that failure was due to a physiological immaturity. One must admit that there was little to controvert such a view.

These studies ignore or overlook the fact that infections in the young do engender immunity. There is and has been little or no question but that the resultant immunity is relatively as satisfactory as that developed in older persons by the same infection. Also there is the established fact that vaccination of the young infant with cowpox successfully immunizes him against smallpox.

The highly successful reintroduction in this country of pertussis immunization by Sauer [2] in 1933, following the fundamental studies of Madsen [3] in the Faroe Islands and those pertaining to phase degeneration of Hemophilus pertussis by Leslie and Gardner,[4] made necessary a reevaluation of the concept that immunity is a maturation process.

The finding that phase I bacteria were capable of eliciting protective immunity immediately raised the question as to whether or not the young infant, who bears the impact of serious morbidity and mortality from pertussis, could be immunized.

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1. Baumgartner, L.: The Relationship of Age to Immunological Reactions, Yale J. Biol. & Med. **6**:403 (March) 1934.

2. Sauer, L. W.: Whooping Cough: A Study in Immunization, J. A. M. A. **100**:239 (Jan. 28) 1933.

3. Madsen, T.: Whooping Cough: Its Bacteriology, Diagnosis, Prevention and Treatment, Boston M. & S. J. **192**:50 (Jan.) 1925.

4. Leslie, P. H., and Gardner, A. D.: Phases of Haemophilus Pertussis. J. Hyg. **31**:423 (July) 1931.

Sauer [5] was the first to explore this question. On the basis of protection lasting over a period of several years he was able to show that the infants vaccinated at 7 or more months had only 10 per cent as much pertussis as did controls and that infants immunized before 3 months of age had 55 per cent as much pertussis as did the controls. He strongly advocated immunization only after 7 months of age. In 1942 Peterson and associates [6] were able to demonstrate that young infants would develop antibody after systematic injection with phase I pertussis vaccine, indicating that even the youngest infant could be protected against whooping cough. The studies of Sako in 1945 [7] and later of Sauer [8] confirmed these findings and demonstrated that protection as well as the development of antibody could be demonstrated. Since then other studies [9] have confirmed and elaborated this thesis.

The demonstration that infants could respond to pertussis vaccine and the introduction of complex vaccine-toxoid mixtures have raised the question as to whether or not diphtheria immunity could be developed in the young infants. Many of the early studies regarding the ability of infants to respond to diphtheria were carried out with toxin-antitoxin mixtures which were grossly inadequate, and the Schick test was the only index of response used.

In October 1944, we initiated a study of the use of a combined vaccine preparation in the immunization of young infants. The study was projected to run a minimum of six years, and it was hoped that many questions relating to immunizations might in time be answered. Preliminary reports of these studies were made in 1946,[9c] 1948 and 1949.[10]

II. PROCEDURES AND MATERIALS

Infants were admitted to the study when they came to the Vanderbilt University Hospital Well Baby Clinic for their first check-up, usually at the age of 6 weeks but occasionally as early as 4 weeks. Older infants and children not previously vaccinated who had negative histories regarding disease were also admitted to obtain comparable older age groups. In all, some 2,000 children were admitted, of whom 573 have been followed for 13 months or more and have had one or more postimmunization serologic studies. The group was selected only by the willingness of the parents to enter their children in the study after the procedure was outlined and the fact that the children have returned for at least one postimmunization observation.

5. Sauer, L. W.: The Age Factor in Active Immunization Against Whooping Cough, Am. J. Path. **17**:719 (Sept.) 1941.

6. Keller, A. E.; Peterson, J. C., and Densen, P. M.: Opsonocytophagic Reaction to Whooping Cough Vaccination, Am. J. Pub. Health **32**:240 (March) 1942.

7. Sako, W.; Treuting, W. L.; Witt, D. B., and Nichamin, S. J.: Early Immunization Against Pertussis with Alum Precipitated Vaccine, J. A. M. A. **127**:379 (Feb. 17) 1945.

8. Sauer, L. W.: Whooping Cough Prevention and Treatment, M. Clin. North America **30**:45 (Jan.) 1946.

9. (*a*) Waddell, W. W., and L'Engle, C. S., Jr.: Immune Response to Early Administration of Pertussis Vaccine, J. Pediat. **29**:487 (Oct.) 1946. (*b*) Sako, W.: Studies on Pertussis Immunization, ibid. **30**:29 (Jan.) 1947. (*c*) Peterson, J. C.: The Capacity of Young Infants to Form Antibody, Am. J. Dis. Child. **73**:238 (Feb.) 1947. (*d*) Adams, J. M.; Kimbal, A. G., and Adams, F. H.: Early Immunization for Pertussis, ibid. **74**:10 (July) 1947. (*e*) di Sant' Agnese, P. A.: Combined Immunization Against Diphtheria, Tetanus, Pertussis in Newborn Infants: I. Production of Antibodies in Early Infancy, Pediatrics **3**:20 (Jan.) 1949.

10. Read before the Brooklyn Academy of Pediatrics, Brooklyn, February 1948; the American Public Health Association, New York, October 1949; and the Southern Medical Association, Cincinnati, November 1949.

The immunization procedure consisted of a primary immunization and one or more secondary or booster immunizations, the first of these being given 13 months after primary immunization and the subsequent booster immunizations at two year intervals.

The primary course consisted of three injections of vaccine complex at intervals of six weeks or over a total period of three months. The vaccine complex was an aluminum hydroxide–adsorbed diphtheria, tetanus and pertussis mixture or aluminum hydroxide–adsorbed pertussis vaccine to which we added 0.3 cc. of standard typhoid vaccine at the time of injection. The routine also included vaccination against smallpox when the first injection was made and revaccination at subsequent visits if the first attempt was not successful.

TABLE 1.—*Antigenic Components of Vaccination Procedure*

Injection	Age	Diphtheria Toxoid, Lf * Doses	Tetanus Toxoid, MLD †	Phase I Pertussis, No. of Bacteria ‡	Standard Typhoid Vaccine, Cc.
1	6 wk. or more §	30±	100,000	20,000,000,000	0.3
2	3 mo. or more	....	.....	40,000,000,000 ¶	0.3
3	4½ mo. or more	30±	100,000	20,000,000,000	0.3
	Total in primary course	60	200,000	80,000,000,000	0.9
4 and thereafter	17½ mo. or more	15±	50,000	10,000,000,000	0.3

† Minimum lethal dose.
‡ All vaccines used in the study were supplied by Cutter Laboratories, of Berkeley, Calif. The diphtheria-tetanus-pertussis mixture was from various lots of their commercial vaccine.
§ Occasionally at less than 6 weeks.
¶ The pertussis vaccine containing 40,000,000,000 adsorbed organisms given at the second injection was a special vaccine prepared at our request.

TABLE 2.—*Plan of Study*

Study, Mo.	Injection	Injection Site	Serum Sample
0	1st injection.....	LL thigh	1
1½	2d injection.....	RL thigh	..
3	3d injection.....	LU thigh	2
6	.....	.....	3
9	.....	.....	4
12	.....	.....	5
16	1st secondary injection.....	RU thigh	6
16¼	.....	.....	6*
20	.....	.....	7
24	.....	.....	8
30	.....	.....	9
36	2d secondary injection.....	LU arm	10
36¼	.....	.....	10*
48	.....	.....	11
60	3d secondary injection.....	RU arm	12
60¼	.....	.....	12*
72	.....	.....	13

* These serum samples were taken a week after the secondary immunization to observe the immediate response.

The antigenic mixtures and the method of their employment are detailed in table 1.

Serum samples for antibody titration were obtained at the time of the first and third injections and at three month intervals for nine months before the booster immunization and at four to twelve months after the secondary injections.

All injections were made in a prescribed routine to avoid superimposition. The outline of the routine and the study is shown in table 2.

Serum samples were titrated for diphtheria and toxin values by the skin test method of Kellogg.[11] Early in the study 0.03 unit was the lowest antitoxin titration carried out, but later

11. Kellogg, W. H.: Test for Diphtheria Immunity and Susceptibility, J. A. M. A. **78**:1782 (June 10) 1922.

titrations were carried to a level of 0.003 unit, the level now generally accepted as being equivalent to the Schick-negative state.

The early titrations of the tetanus antitoxin were made with use of guinea pigs, but the prohibitive cost of this method necessitated a change to the use of mice according to the method recommended by the New York State Department of Health.

The pertussis agglutinations early were carried out according to the method of Miller and others,[12] but later a modification of the technic of Flosdorf and others[13] was employed, after duplicate titrations had shown satisfactory parallelism.

All serologic studies were carried out by the Biologic Control Department of Cutter Laboratories.

While it cannot be concluded that a given level of antibody will give, in any particular person, a partial or complete protective immunity, the equivalence of serum antibody to protection is satisfactory for use as a working tool. In these studies we were also concerned with a study of the factors which modify the serologic response as well as with protection, and for these purposes antibody demonstrations by any consistent technic will give satisfactory values. No attempt has been made to correlate protection with the antibody responses. Field studies were considered, but limitations of staff and the wide area represented by the group made this impracticable.

The first objective in the study has been an evaluation of the ability of the infant less than 3 months of age to produce antibody to the individual components of the antigenic complex given.

The question of the use of complex antigen mixtures rather than individual antigens has received increasing attention since the work of Zoeller and Ramon.[14] The simplification of the immunization routine with these mixtures makes their use highly desirable if they yield satisfactory responses and do not provoke excessive reactions. It seems adequately established[15] that complex mixtures generally induce responses superior to those evoked by a single antigen.

III. REACTIONS

It was anticipated that reactions to this vaccine complex might be severe because of the amount of foreign material being used, but it became apparent almost immediately that the reactions were not appreciably greater than those encountered in using unprecipitated pertussis vaccine containing 20,000,000,000 organisms. It

12. Miller, J. J.; Silverberg, R. J.; Saito, T. M., and Humber, J. B.: Agglutinative Reaction for Hemophilus Pertussis: Its Relation to Clinical Immunization, J. Pediat. **22**:644 (June) 1943.

13. Flosdorf, E. W.; McGuinness, A. C.; Kimball, A. C., and Armstrong, J. G.: Studies with H. Pertussis: Preparation and Assay of Hyperimmune Human Serum, J. Pediat. **19**:638 (Nov.) 1941.

14. Zoeller, C., and Ramon, G.: Les conditions biologiques de la vaccination antitétanic par l'anatoxin chez l'homme, Bull. Acad. de méd., Paris **95**:104 (Feb. 2) 1926.

15. Ramon, G.: Mixed Vaccinations, Internat. Clin. **1**:241 (March) 1939. Bell, J. A.: Diphtheria Immunization: Use of Alum-Precipitated Mixture of Pertussis Vaccine and Diphtheria Toxoid, J. A. M. A. **137**:1009 (July 17) 1948. Ordman, D., and Grasset, E.: Combined Pertussis-Diphtheria Prophylactic Antigens Used in Combination: Experimental Study to Determine Specific Immunizing Value of These Antigens Used in Combination, J. Hyg. **46**:117 (July) 1948. Greenburg, L., and Fleming, D. S.: Immunizing Efficiency of Diphtheria Toxoid When Combined with Various Antigens, Canad. J. Pub. Health **39**:131 (April) 1948. di Sant' Agnese, P. A.: Combined Immunization Against Diphtheria, Tetanus and Pertussis in Children Over 3 Months of Age, Including an Evaluation of 2 Immunizing Agents, J. Pediat. **31**:251 (Sept.) 1947.

has, however, been a regular policy to anticipate reactions, to warn the parents that the child will have fever and malaise for 12 to 48 hours and to suggest that acetylsalicylic acid in 75 mg. doses be given to the infant before bedtime on the day of the injection and at other times for irritability for as many as three or four doses.

Less than a dozen abscesses or persistent nodules have been encountered in the infants who received the more than 6,000 injections given to date. Small indurated areas do commonly persist for six to eight weeks after the injection of the complete mixture. The local area is usually not painful more than three to four days. Later and relatively uncommonly, there may be minimal subcutaneous fibrosis with the formation of a small dimple at the injection site.

No adverse reactions to the smallpox vaccination have been encountered. Only very rarely do the parents note systemic reactions of any degree in association with this procedure.

Febrile convulsive seizures have occurred in five children, none of which followed the second injection. Usually there has been a family history of others having had febrile seizures. In one instance the child has subsequently had other seizures; in this case there was a family history of epilepsy. The seizures have occurred two to three hours after, rather than immediately after, the injections.

To minimize the local reactions, injections were given deep in the subcutaneous tissue and gentle massage was used to disperse the vaccine depot. A 1 inch (2.5 cm.) 25 gage needle was used. The plunger was routinely drawn back to minimize risk of intravascular injection.

The febrile responses following injection have not been followed by thermometric observations. In approximately 40 per cent of the children the reactions are reported by the mothers as not being noticeable. Another 40 per cent have mild to moderate fever the evening of the injection and about 20 per cent have fever for more than 12 hours, usually not more than 24 hours but occasionally for 48 to 72 hours.

IV. ANTIBODY RESPONSES TO PERTUSSIS IMMUNIZATION

The fact that it is the infant who is most seriously affected by pertussis makes the need for finding an adequate method of protecting the infant one of the prime reasons for initiating these studies. One earlier study merely showed a capacity to respond and did not indicate the best method of giving the vaccine. The introduction of alum-precipitated vaccines seemed to be a step which would overcome some of the difficulties attendant on our previous practice, the use of 100,000,000,000 organisms given in five weekly injections.

Early unpublished studies on the use of alum-precipitated pertussis vaccine had indicated that 60,000,000,000 phase I organisms would not yield what we deemed to be a satisfactory antibody response. In setting up the current investigation we therefore chose to use 80,000,000,000 adsorbed organisms. To secure this bacterial dose it was necessary to obtain a special 40,000,000,000 organisms per milliliter adsorbed vaccine to be given at the second injection.

No accurate practical method was available to determine exposure and possible disease; so no attempt has been made to evaluate field protection among the vaccinated group.

Immediate Responses.—The immediate agglutinin responses to pertussis vaccination for the group as a whole are shown in table 3, and the quartiles of the distribution of responses are summarized in chart 1.

The immediate agglutinin responses for the group as a whole were very satisfactory. However, three months after the completion of the primary vaccination course 14 per cent of the children showed an agglutinin titer of less than 1 : 50, the

TABLE 3.—*H. Pertussis Agglutinin Titers Following Vaccination Among 573 Infants and Young Children*

Agglutinin Titers	Test: Before Injection No.	%	At End of Injection No.	%	Months After Primary Immunization: 3 No.	%	6 No.	%	9 No.	%	13* No.	%	13¼ No.	%	17 No.	%	21 No.	%	27 No.	%	33 No.	%
1/3,200	10	2.2	106	29.5	188	39.9	121	40.1	64	31.2	73	33.5	18	78.3	44	37.9	9	37.5	10	41.7	9	34.6
1/1,600	8	1.7	46	12.6	68	14.4	48	16.0	33	16.1	36	16.5	2	8.7	31	26.7	1	4.2	1	4.2	6	23.1
1/800	4	0.9	35	9.6	56	11.9	37	12.2	22	10.7	30	13.8	0	....	14	12.1	5	20.8	3	12.5	3	11.5
1/400	9	1.9	31	8.5	33	7.0	27	8.9	22	10.7	14	6.4	0	....	7	6.0	4	16.7	2	8.3	3	11.5
1/200	18	3.9	41	11.2	41	8.7	18	6.0	12	5.8	18	8.3	0	....	3	2.6	1	4.2	2	8.3	1	3.8
1/100	14	3.0	17	4.6	15	3.2	7	2.3	3	1.5	0	....	0	....	1	0.9	0	....	1	4.2	0	....
1/50	10	2.2	7	1.9	4	0.8	2	0.7	1	0.5	3	1.4	0	....	0	....	0	....	0	....	0	....
< 1/50	389	84.2	81	22.2	66	14.0	42	13.9	48	23.4	44	20.2	3	13.0	16	13.8	4	16.7	5	20.8	4	15.4
Total	462	100.0	364	100.0	471	99.9	302	100.0	205	99.9	218	100.0	23	100.0	116	100.0	24	100.1	24	100.0	26	99.9
Total < 1/400	431	93.3	146	39.9	126	26.7	69	22.9	64	31.2	65	29.9	3	13.0	20	17.3	5	20.8	8	33.3	5	19.2

* At the end of 13 months a secondary injection, 10,000,000,000 phase I H. pertussis organisms, was given.

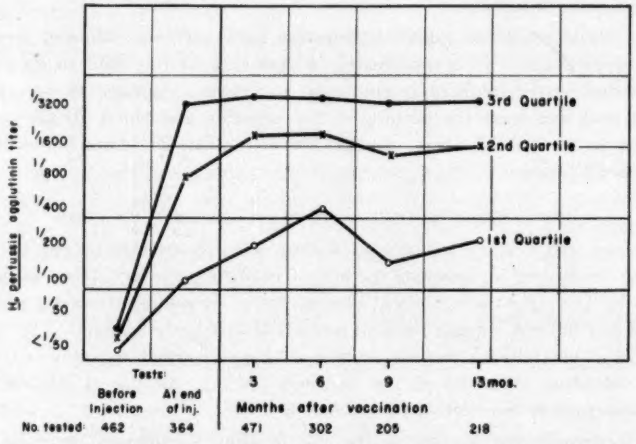

Chart 1.—H. pertussis agglutinin titers following primary vaccination among 573 infants and young children, by quartiles.

least amount measured. Similarly there were 13.8 per cent who showed no titratable agglutinin following the secondary, or booster, injection, given 13 months after the completion of the primary vaccination.

If one assumes from the studies of Miller and of Sako and the assumptions of di Sant' Agnese that agglutinin titers of 1 : 400 are the level affording protection, then 73.3 per cent of the group attained protective levels at the time that one would

expect the titers to be high. In general these responses are superior to those reported by Sako and others [7] for children of any age group. In their studies they used fluid vaccines, vaccines adsorbed on potassium alum and vaccines adsorbed on aluminum hydroxide. These responses are nearly equivalent to those obtained by di Sant' Agnese,[9c] who used vaccine containing 100,000,000,000 unadsorbed organisms or 50,000,000,000 adsorbed organisms in an older age group. Our

TABLE 4.—*H. Pertussis Agglutinin Responses of Various Age Groups Three Months After the Primary Vaccination*

	Age at Which Immunizations Were Initiated									
	< 3 Mo.		3 to 5 Mo.		6 to 11 Mo.		> 12 Mo.		Total	
Agglutinin Titers	No.	%	No.	%	No.	%	No.	%	No.	%
1/3,200	100	34.6	39	44.3	24	55.8	25	49.0	188	39.9
1/1,600	47	16.3	9	10.2	7	16.3	5	9.8	68	14.4
1/800	38	13.5	13	14.8	2	4.6	2	3.9	56	11.9
1/400	19	6.6	4	4.5	5	11.6	5	9.8	33	7.0
1/200	26	9.0	11	12.5	0	....	4	7.8	41	8.7
1/100	10	3.5	2	2.3	2	4.6	1	2.0	15	3.2
1/50	2	0.7	0	....	0	....	2	3.9	4	0.8
< 1/50	46	15.9	10	11.4	3	7.0	7	13.7	66	14.0
Total	288	100.0	88	100.0	43	99.9	51	99.9	471	99.9
Total < 1/400	84	29.1	23	26.2	5	11.6	14	27.4	126	26.7

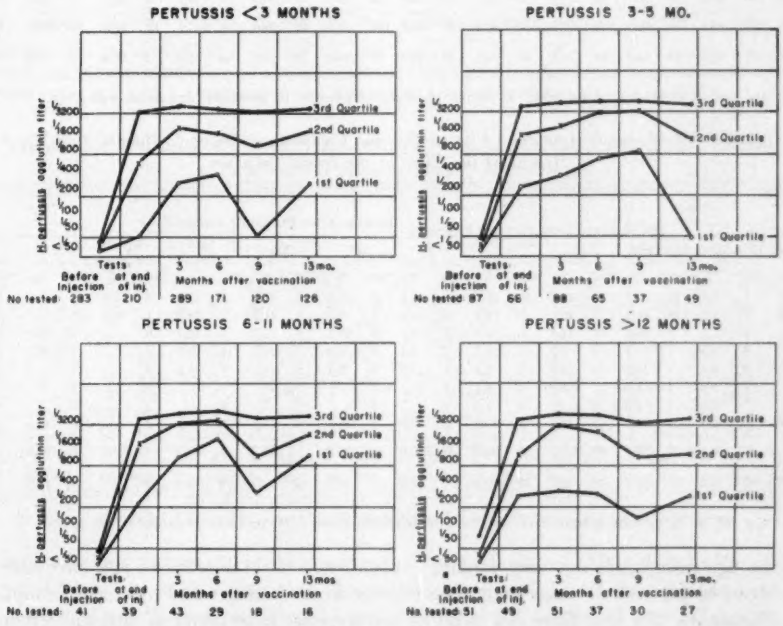

Chart 2.—H. pertussis agglutinins following primary vaccination according to the age at which injections were initiated, by quartiles.

relatively young age group showed a definitely better response than did the young infants of di Sant' Agnese, who received 50,000,000,000 adsorbed organisms from the same basic vaccine as we used.

The Effect of Age on Antibody Responses.—In table 4 is shown a comparison of the responses at 3 months for the various age groups. From this table it is apparent that if one considers only the immediate response and the response above the "protective" levels, agglutination of 1:400 or higher, the differences between

TABLE 5.—*H. Pertussis Agglutinin Titers Following Vaccination Among 352 Infants Aged Less than 3 Months at the Time of the Initial Injection*

Agglutinin Titers	Test: Before Injection		Test: At End of Injection		Months After Primary Immunization: 3		6		9		12*		13¼		17		21		27		33	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
1/3,200	8	2.8	54	25.7	100	34.6	51	29.8	30	25.0	37	29.4	7	70.0	29	39.7	5	26.3	5	45.4	5	33.7
1/1,600	2	0.7	23	10.9	47	16.3	34	19.9	21	17.5	28	22.2	0	....	18	24.7	0	....	1	9.1	2	14.3
1/800	2	0.7	20	9.5	39	13.4	25	14.6	14	11.7	15	11.9	0	....	8	11.0	5	25.3	2	18.7	2	14.3
1/400	4	1.4	19	9.0	19	6.6	18	10.5	16	13.3	9	7.1	0	....	5	6.8	4	21.0	0	....	2	14.3
1/200	10	3.5	24	11.4	26	9.0	14	8.2	5	4.2	11	8.7	0	....	2	2.7	1	5.3	1	9.1	0	....
1/100	6	2.1	12	5.7	10	3.5	4	2.3	2	1.7	0	....	0	....	1	1.4	0	....	0	....	0	....
1/50	5	1.8	4	1.9	2	0.7	1	0.6	1	0.8	2	1.6	0	....	0	....	0	....	0	....	0	....
< 1/50	246	86.9	54	25.7	46	15.9	24	14.0	31	25.8	24	19.0	3	30.0	10	13.7	4	21.0	2	18.2	3	21.4
Total	283	99.9	210	99.6	289	100.1	171	99.9	120	100.0	126	99.9	10	100.0	73	100.0	19	99.9	11	100.0	14	100.0
Total < 1/400	267	94.3	94	44.5	84	29.1	43	25.1	39	32.4	37	29.3	3	30.0	13	17.8	5	26.3	3	27.3	3	21.4

* At the end of 13 months a secondary injection, 10,000,000,000 phase I H. pertussis organisms, was given.

TABLE 6.—*H. Pertussis Agglutinin Titers Following Vaccination Among 53 Infants Aged 3 to 5 Months at the Time of the Initial Injection*

Agglutinin Titers	Test: Before Injection		Test: At End of Injection		Months After Primary Immunization: 3		6		9		12*		13¼		17		21		27		33	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
1/3,200	2	2.3	22	33.3	39	44.3	32	49.2	19	51.4	20	40.8	8	88.8	8	33.3	3	75.0	1	20.0	3	42.8
1/1,600	1	1.1	10	15.1	9	10.2	9	13.8	6	16.2	1	2.0	1	11.2	7	29.2	1	25.0	0	....	2	28.5
1/800	0	...	9	13.6	13	14.8	6	9.2	3	8.1	10	20.4	0	....	4	13.7	0	....	1	20.0	1	14.3
1/400	2	2.3	4	6.1	4	4.5	5	7.7	2	5.4	1	2.0	0	....	2	8.3	0	....	1	20.0	0	....
1/200	4	4.6	7	10.6	11	12.5	2	3.1	0	....	3	6.1	0	....	1	4.2	0	....	0	....	0	....
1/100	4	4.6	3	4.5	2	2.3	2	3.1	0	....	0	....	0	....	0	....	0	....	0	....	0	....
1/50	2	2.3	2	3.0	0	....	1	1.5	0	....	0	....	0	....	0	....	0	....	0	....	0	....
< 1/50	72	82.7	9	13.6	10	11.4	8	12.3	7	18.9	14	28.6	0	....	2	8.3	0	....	2	40.0	1	14.3
Total	87	99.9	66	99.8	88	100.0	65	99.9	37	100.0	49	99.9	9	100.0	24	100.0	4	100.0	5	100.0	7	99.9
Total < 1/400	82	94.2	21	31.7	23	26.2	13	20.0	7	18.9	17	34.7	0	....	3	12.4	0	....	2	40.0	1	14.3

* At the end of 13 months a secondary injection, 10,000,000,000 phase I H. pertussis organisms, was given.

the age groups are not very striking. Children 6 to 11 months of age have only about 40 per cent as many poor responses as do the younger and older age groups. During the first year there is a trend for the response to be better in each succeeding older age group as to the number attaining the highest levels and as to failure to respond, a trend reversed with the oldest age group. None of the differences noted are of statistical significance, but the trend for the first year is suggestive.

In tables 5, 6, 7 and 8 are shown the responses to the pertussis vaccination among these various age groups. In chart 2 the distribution of the responses by quartiles for the various age groups is summarized.

Persistence of Antibody After Primary Vaccination.—While the immediate high levels of response are of great importance, it is equally important to consider the persistence of the levels. Inasmuch as all who returned were given secondary injections 13 months after the primary vaccination, we can at this time consider only the persistence during the first 13 months.

Six months after vaccination there was substantially the same degree of "protection" present as at three months and about the same relation between the various

TABLE 7.—*H. Pertussis Agglutinin Titers Following Vaccination Among 53 Infants Aged 6 to 11 Months at the Time of Initial Injection*

Agglutinin Titers	Test: Before Injection		Test: At End of Injection		Months After Primary Immunization: 3		6		9		13*		13¼		17		21		27		33	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
1/3,200	0	...	14	35.9	24	55.8	21	72.4	7	38.9	7	43.7	1	100.0	3	33.3	1	100.0	2	66.6	1	33.3
1/1,600	1	2.4	6	15.4	7	16.3	1	3.4	1	5.5	4	25.0	0	....	4	44.4	0	....	0	....	1	33.3
1/800	2	4.9	3	7.7	2	4.6	3	10.3	2	11.1	2	12.5	0	....	2	22.2	0	....	0	....	0	....
1/400	1	2.4	3	7.7	5	11.6	1	3.4	3	16.7	1	6.2	0	....	0	....	0	....	1	33.3	0	....
1/200	1	2.4	4	10.2	0	....	0	....	2	11.1	0	....	0	....	0	....	0	....	0	....	1	33.3
1/100	1	2.4	1	2.6	2	4.6	1	3.4	0	....	0	....	0	....	0	....	0	....	0	....	0	....
1/50	1	2.4	0	....	0	....	0	....	0	....	1	6.2	0	....	0	....	0	....	0	....	0	....
< 1/50	34	82.9	8	20.5	3	7.0	2	6.9	3	16.7	1	6.2	0	....	0	....	0	....	0	....	0	....
Total	41	99.8	39	100.0	43	99.9	29	99.8	18	100.0	16	99.8	1	100.0	9	99.9	1	100.0	3	99.9	3	99.9
Total < 1/400	37	90.1	13	33.3	5	11.6	3	10.3	5	27.8	2	12.5	0	....	0	....	0	....	0	....	1	33.3

* At the end of 13 months a secondary injection, 10,000,000,000 phase I H. pertussis organisms, was given.

TABLE 8.—*H. Pertussis Agglutinin Titers Following Vaccination Among 66 Young Children Aged 12 Months or More at Time of Initial Injection*

Agglutinin Titers	Test: Before Injection		Test: At End of Injection		Months After Primary Immunization: 3		6		9		13*		13¼		17		27		33	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
1/3,200	0	....	16	32.6	25	49.0	17	45.9	8	26.7	9	33.3	2	66.6	4	40.0	2	40.0	0	....
1/1,600	4	7.8	7	14.2	5	9.8	4	10.8	5	16.7	3	11.1	1	33.3	2	20.0	0	....	1	50.0
1/800	0	....	3	6.1	2	3.9	3	8.1	3	10.0	3	11.1	0	....	0	....	0	....	0	....
1/400	2	3.9	5	10.2	5	9.8	3	8.1	1	3.3	3	11.1	0	....	0	....	0	....	1	50.0
1/200	3	5.9	6	12.2	4	7.8	2	5.4	5	16.7	4	14.8	0	....	0	....	1	20.0	0	....
1/100	3	5.9	1	2.0	1	2.0	0	....	1	3.3	0	....	0	....	0	....	1	20.0	0	....
1/50	2	3.9	1	2.0	2	3.9	0	....	0	....	0	....	0	....	0	....	0	....	0	....
< 1/50	37	72.6	10	20.4	7	13.7	8	21.6	7	23.3	5	18.5	0	....	4	40.0	1	20.0	0	....
Total	51	100.0	49	99.7	51	99.9	37	99.9	30	100.0	27	99.9	3	99.9	10	100.0	5	100.0	2	100.0
Total < 1/400	45	88.3	18	36.6	14	27.4	10	27.0	13	43.3	9	33.3	0	....	4	40.0	3	60.0	0	....

* At the end of 13 months a secondary injection, 10,000,000,000 phase I H. pertussis organisms, was given.

ages. At nine months the agglutinin levels of more infants fell to less than 1 : 50—26 per cent of the infants less than 3 months of age and 19, 16 and 23 per cent respectively of those 3 to 5, 6 to 11 and more than 12 months of age. However, the number having "protective" levels was 60 per cent or more for all age groups. The observations for the various age groups at the 13 month period are summarized and compared in table 9.

Protective levels were maintained by 65 per cent or more of the children in each group, indicating that the procedure used was relatively satisfactory and that

the immunization of infants at 6 weeks is entirely practicable both from the viewpoint of the immediate response and from the viewpoint of the persistence of immunity through the 13 months of observation.

Effect of Passive Immunity.—The fact that younger infants do show some quantitative differences from those of the older groups suggests examination of other factors.

Greengard and Bernstein [16] and more recently Cooke and Jones [17] and di Sant' Agnese [18] have shown that passive immunity interferes with the development of

TABLE 9.—*H. Pertussis Agglutinin Levels Present Among Various Age Groups 13 Months After Primary Vaccination*

	Age at Which Immunizations Were Initiated									
	< 3 Mo.		3 to 5 Mo.		6 to 12 Mo.		> 12 Mo.		Total	
Agglutinin Titers	No.	%	No.	%	No.	%	No.	%	No.	%
1/3,200	37	29.4	20	40.8	7	43.7	9	33.3	73	33.5
1/1,600	28	22.2	1	2.0	4	25.0	3	11.1	36	16.5
1/800	15	11.9	10	20.4	2	12.4	3	11.1	30	13.8
1/400	9	7.1	1	2.0	1	6.2	3	11.1	14	6.4
1/200	11	8.7	3	6.1	0	....	4	14.8	18	8.2
1/100	0	....	0	....	0	....	0	....	0	....
1/50	2	1.6	0	....	1	6.2	0	....	3	1.4
< 1/50	24	19.0	14	28.6	1	6.2	5	18.5	44	20.2
Total	126	100.0	49	100.0	16	100.0	27	100.0	218	100.0
Total < 1/400	37	29.3	17	34.7	2	12.4	9	33.3	65	29.8

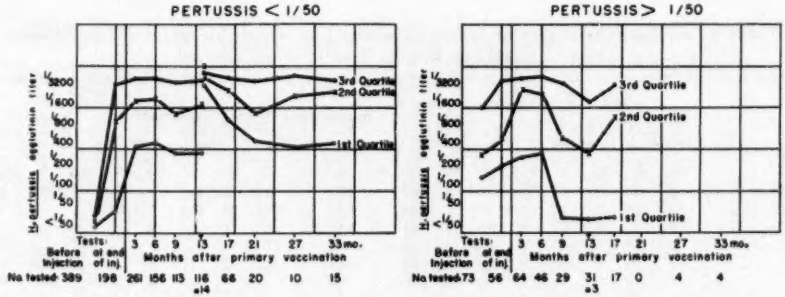

Chart 3.—H. pertussis agglutinin titers following primary and booster immunizations among infants and children with and without preimmunization antibody. The arrow indicates the secondary injection, 10,000,000,000 phase I H. pertussis organisms, and the asterisk, one week after the secondary injection.

16. Greengard, J., and Bernstein, H.: Passive Immunity in Infants and Their Response to Diphtheria Toxoid: Preliminary Report, J. A. M. A. **105**:341 (Aug. 3) 1935.

17. (*a*) Cooke, J. V., and Jones, F. G.: Duration of Passive Tetanus Immunity and Its Effect on Active Immunization with Tetanus Toxoid, J. A. M. A. **121**:1201 (April 10) 1943. (*b*) Cooke, J. V.: Antibody Formation in Early Infancy Against Diphtheria and Tetanus Toxoids, J. Pediat. **33**:141, (Aug.) 1948.

18. di Sant' Agnese, P. A.: Combined Immunization Against Diphtheria, Tetanus and Pertussis in Newborn Infants: II. Duration of Antibody Levels and Antibody Titers After Booster Dose; Effect of Passive Immunity to Diphtheria on Active Immunization with Diphtheria Toxoid, Pediatrics **3**:181 (Feb.) 1949.

active immunity from a given antigenic stimulus. Seventy-three, or 15.8 per cent, of the children of our study group showed pertussis agglutinins in the preimmunization titration. In each age group 13 to 28 per cent of the children has some preimmunization agglutinins. In some of the older children these agglutinins were probably actively rather than passively acquired.

The agglutinin responses of these without and with preimmunization agglutinins are shown in tables 10 and 11 respectively, and the distributions are summarized

TABLE 10.—*H. Pertussis Agglutinin Titers Following Primary and Booster Immunizations Among 389 Infants and Children Who Had No Antibody When Injections Were Initiated*

Agglutinin Titers	Test: Before Injection		Test: At End of Injection		Months After Primary Immunization: 3		6		9		13*		13¼		17		21		27		33	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
1/3,200	0	....	71	27.7	125	39.5	84	41.4	45	31.7	53	37.3	14	77.8	35	43.7	8	38.1	8	47.0	7	35.0
1/1,600	0	....	38	14.8	49	15.5	30	14.8	21	14.8	21	14.8	1	5.5	21	26.2	1	4.8	1	5.9	6	30.0
1/800	0	....	28	10.9	44	13.9	24	11.8	19	13.3	20	14.1	0	....	7	8.7	5	23.8	2	11.8	0	....
1/400	0	....	19	7.4	21	6.6	21	10.3	20	14.1	11	7.7	0	....	6	7.5	3	14.3	2	11.8	3	15.0
1/200	0	....	21	8.2	27	8.5	12	5.9	8	5.6	8	5.6	0	....	2	2.5	0	....	1	5.9	1	5.0
1/100	0	....	9	3.5	7	2.2	5	2.4	2	1.4	0	....	0	....	1	1.2	0	....	1	5.9	0	....
1/50	0	....	6	2.3	2	0.6	1	0.5	0	....	1	0.7	0	....	0	....	0	....	0	....	0	....
< 1/50	389	100.0	64	25.0	41	13.0	26	12.8	27	19.0	28	19.7	3	16.7	8	10.0	4	19.0	2	1.8	3	15.0
Total	389	100.0	256	99.8	316	99.8	203	99.9	142	99.9	142	99.9	18	100.0	80	99.8	21	100.0	17	100.1	20	100.0
Total < 1/400	389	100.0	100	39.0	77	24.3	44	21.6	37	26.0	37	21.6	3	16.7	11	13.2	4	19.0	4	23.6	4	20.0

* At the end of 13 months a secondary injection, 10,000,000,000 phase I H. pertussis organisms, was given.

TABLE 11.—*H. Pertussis Agglutinin Titers Following Primary and Secondary Vaccination Among 73 Infants and Young Children with Detectable Antibody When Injections Were Initiated*

Agglutinin Titers	Test: Before Injection		Test: At End of Injection		Months After Primary Immunization: 3		6		9		13*		13¼		17		27		33	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
1/3,200	10	13.7	19	33.9	31	48.4	21	45.6	9	31.0	7	22.6	2	66.7	5	29.4	1	25.0	1	25.0
1/1,600	8	11.0	5	8.9	8	12.5	5	10.9	4	13.8	1	3.2	1	33.3	2	11.8	0	....	0	....
1/800	4	5.5	1	1.8	1	1.6	4	8.7	1	3.4	4	12.9	0	....	3	17.6	1	25.0	2	50.0
1/400	9	12.3	6	10.7	5	7.8	4	8.7	1	3.4	3	9.7	0	....	1	5.9	0	...	0	....
1/200	18	24.7	14	25.0	7	10.9	3	6.5	3	10.3	2	6.4	0	...	0	....	0	....	0	....
1/100	14	19.1	5	8.9	2	3.1	0	....	0	....	0	....	0	....	0	....	0	....	0	....
1/50	10	13.7	1	1.8	2	3.1	1	2.2	1	3.4	2	6.4	0	....	0	....	0	....	0	....
< 1/50	0	....	5	8.9	8	12.5	8	17.4	10	34.5	12	38.7	0	....	6	35.3	2	50.0	1	25.0
Total	73	100.0	56	99.9	64	99.9	46	100.0	29	99.8	31	99.9	3	100.0	17	100.0	4	100.0	4	100.0
Total < 1/400	42	57.5	25	44.6	19	29.6	12	26.1	14	48.2	16	41.5	0	....	6	35.3	2	50.0	1	25.0

* At the end of 13 months a secondary injection, 10,000,000,000 phase I H. pertussis organisms, was given.

in chart 3. Only slight differences are observed in the period three months after immunization. The number with low levels of response was only slightly greater among those with preimmunization antibody, and paradoxically there was a higher per cent of the group which showed high levels of response. These differences are too small to be of significance. This paradoxical response may be due to the fact that the group with preimmunization agglutinins included some children in whom these represented active rather than passive immunity. However, 13 months after immunization there were more among those with preimmunization antibody who

had titers below the protective level and also fewer who showed high levels of antibody. These observations are shown in table 12. These differences are statistically significant. They show that while passive immunity did not materially inhibit the immediate production of antibody the immunity is less well maintained among those with preimmunization antibody.

The studies of Cooke and Jones [17a] showed not only that passive immunity prevented satisfactory antibody responses but that it also inhibited the development

TABLE 12.—*H. Pertussis Agglutinins Among Infants and Children Without and With "Passive" Immunity When the Injections Were Initiated, Three and Thirteen Months After Vaccination*

	Preimmunization Agglutinin Titers							
	3 Months After Vaccination				13 Months After Vaccination			
	< 1/50		> 1/50		< 1/50		> 1/50	
Agglutinin Titers	No.	%	No.	%	No.	%	No.	%
1/3,200	125	39.5	31	48.4	53	37.3	7	22.6
1/1,600	49	15.5	8	12.5	21	14.8	1	3.2
1/800	44	13.9	1	1.6	20	14.1	4	12.9
1/400	21	6.6	5	7.8	11	7.7	3	9.7
1/200	27	8.5	7	10.9	8	5.6	2	6.4
1/100	7	2.2	2	3.1	0	....	0	....
1/50	2	0.6	2	3.1	1	0.7	2	6.4
< 1/50	41	13.0	8	12.5	28	19.7	12	38.7
Total	316	99.8	64	99.9	142	99.9	31	99.9
Total < 1/400	77	24.3	19	29.6	37	26.0	16	51.6

TABLE 13.—*H. Pertussis Agglutinin Levels Following Primary Vaccination Among 246 Infants Aged Less than 3 Months and Who Had No Antibody When Injections Were Initiated*

	Test				Months After Primary Immunization											
	Before Injection		At End of Injection		3		6		9		13*		13¼		17	
Agglutinin Titers	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
1/3,200	0	....	37	24.3	69	34.3	33	30.0	23	26.7	26	32.1	6	66.7	23	46.0
1/1,600	0	....	20	13.2	37	18.4	23	20.9	15	17.4	17	21.0	0	....	13	26.0
1/800	0	....	16	10.5	29	14.4	14	12.7	13	15.1	10	12.3	0	....	3	6.0
1/400	0	....	10	6.6	15	7.5	14	12.7	15	17.4	8	9.9	0	....	4	8.0
1/200	0	....	13	8.6	16	8.0	9	8.2	3	3.5	5	6.2	0	....	1	2.0
1/100	0	....	8	5.3	6	3.0	3	2.7	1	1.2	0	....	0	....	1	2.0
1/50	0	....	3	2.0	1	0.5	0	....	0	....	0	....	0	....	0	....
< 1/50	246	100.0	45	29.6	28	13.9	14	12.7	16	18.6	15	18.5	3	33.3	5	10.0
Total	246	100.0	152	100.1	201	100.0	110	99.9	86	99.9	81	100.0	9	100.0	50	100.0
Total < 1/400	246	100.0	69	45.5	51	25.4	26	23.6	20	23.3	20	24.7	3	33.3	7	14.0

* At the end of 13 months a secondary injection, 10,000,000,000 phase I H. pertussis organisms, was given.

of primary immunity from the viewpoint of the person's capacity to respond to secondary immunizations. Chart 3 shows that infants and children with preimmunization antibody responded less well to secondary immunization. The numbers are too small to show a statistically significant difference, but this consistent trend is highly suggestive.

Relation of Aging to Inhibition from "Passive" Immunity.—It was also apparent in Cooke's [17b] study that the presence of passive immunity was a greater obstacle

to the response to diphtheria toxoid when it was present among very young infants than when present in older infants.

There were 37 infants less than 3 months of age, 13 per cent of this age group, who showed some H. pertussis agglutinins. Tables 13 and 14 show the responses among the infants less than 3 months without and with preimmunization agglutinins. From these tables it can be seen that among those without preimmunization

TABLE 14.—*H. Pertussis Agglutinin Levels Following Primary Vaccination Among 37 Infants Aged Less than 3 Months and Having Some Antibody when Injections Were Initiated*

Agglutinin Titers	Test: Before Injection		Test: At End of Injection		Months After Primary Immunization: 3		6		9		13*		13¼		17	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
1/3,200	8	21.6	9	29.0	16	51.6	9	37.5	3	18.8	4	22.2	1	100.0	3	30.0
1/1,600	2	5.4	1	3.2	2	6.5	2	8.3	1	6.2	1	5.6	0	....	1	10.0
1/800	2	5.4	1	3.2	0	....	2	8.3	0	....	0	....	0	....	1	10.0
1/400	4	10.8	5	16.1	1	3.2	2	8.3	1	6.2	1	5.6	0	....	1	10.0
1/200	10	27.0	8	25.8	4	12.9	3	12.5	2	12.5	2	11.1	0	....	0	....
1/100	6	16.2	3	9.7	0	....	0	....	0	....	0	....	0	....	0	....
1/50	5	13.5	1	3.2	1	3.2	1	4.2	1	6.2	2	11.1	0	....	0	....
< 1/50	0	....	3	9.7	7	22.6	5	20.8	8	50.0	8	44.4	0	....	4	40.0
Total	37	99.9	31	99.9	31	100.0	24	99.9	16	99.9	18	100.0	1	100.0	10	100.0
Total < 1/400	21	56.7	15	48.4	12	48.7	9	37.5	11	68.7	12	66.6	0	....	4	40.0

* At the end of 13 months a secondary injection, 10,000,000,000 phase I H. pertussis organisms, was given.

TABLE 15.—*H. Pertussis Agglutinins at Three Months and Thirteen Months After Vaccination Among Infants Without and With Passive Immunity and Who Were Less than 3 Months of Age when Injections Were Initiated*

Agglutinin Titers	Preimmunization Agglutinin Titers: 3 Months After Immunization: < 1/50		> 1/50		13 Months After Immunization: <1/50		> 1/50	
	No.	%	No.	%	No.	%	No.	%
1/3,200	69	34.3	16	51.6	20	32.1	4	22.2
1/1,600	37	18.4	2	6.5	17	21.0	1	5.6
1/800	29	14.4	0	....	10	12.3	0	....
1/400	15	7.5	1	3.2	8	9.9	1	5.6
1/200	16	8.0	4	12.9	5	6.2	2	11.1
1/100	6	3.0	0	....	0	....	0	....
1/50	1	0.5	1	3.2	0	....	2	11.1
< 1/50	28	13.9	7	22.6	15	18.5	8	44.4
Total	201	100.0	31	100.0	81	100.0	18	100.0
Total < 1/400	51	25.4	12	38.7	20	24.7	12	66.7

agglutinins at three months there were only 14 per cent who failed to show some response after immunization and 34 per cent who attained a maximum response, while among those with preimmunization antibody 23 per cent failed to show some response and 51 per cent attained the maximum titer. These findings indicate that in the youngest group passive immunity may have some inhibitory influence on the antibody response.

More striking than this difference in the immediate response is the fact that nine and 13 months after immunization 75 per cent of those without preimmuniza-

tion agglutinins still had protective levels, while only 31 and 33 per cent of those with preimmunization agglutinins were protected. These significant differences for the age group less than 3 months are summarized in table 15 and in chart 4, which also shows the quartile distributions for the older group.

Tables 16 and 17, which show the agglutinin values for children older than 3 months prior to immunization according to their preimmunization status, are

TABLE 16.—*H. Pertussis Agglutinin Levels Following Primary Vaccination Among 143 Infants and Young Children Aged More than 3 Months and Having No Antibody When Injections Were Initiated*

Agglutinin Titers	Test: Before Injection		Test: At End of Injection		Months After Primary Immunization: 3		6		9		13*		13¼		17	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
1/3,200	0	....	34	32.7	56	49.1	51	54.8	22	39.3	27	44.2	8	88.8	12	40.0
1/1,600	0	....	18	17.3	11	9.6	7	7.5	6	10.7	4	6.6	1	11.2	8	26.7
1/800	0	....	12	11.5	15	13.0	10	10.7	6	10.7	10	16.4	0	....	4	13.3
1/400	0	....	9	8.6	6	5.3	7	7.5	5	8.9	3	4.9	0	....	2	6.7
1/200	0	....	8	7.7	11	9.6	3	3.2	5	8.9	3	4.9	0	....	1	3.3
1/100	0	....	1	1.0	1	0.9	2	2.1	1	1.8	0	....	0	....	0	....
1/50	0	....	3	2.9	1	0.9	1	1.1	0	....	1	1.6	0	....	0	....
< 1/50	143	100.0	19	18.3	13	11.4	12	12.9	11	19.6	13	21.3	0	....	3	10.0
Total	143	100.0	104	100.0	114	99.9	93	99.8	56	99.9	61	99.9	9	100.0	30	100.0
Total < 1/400	143	100.0	31	29.9	26	22.8	17	19.3	17	30.3	17	27.8	0	....	4	13.3

* At the end of 13 months a secondary injection, 10,000,000,000 phase I H. pertussis organisms, was given.

TABLE 17.—*H. Pertussis Agglutinin Levels Following Primary Vaccination Among 36 Infants Aged More than 3 Months and Having Some Antibody When Injections Were Initiated*

Agglutinin Titers	Test: At End of Injection		Months After Primary Immunization: 3		6		9		13*		13¼		17	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
1/3,200	10	40.0	15	45.4	12	54.4	6	46.1	3	23.1	1	50.0	2	28.6
1/1,600	4	16.0	6	18.7	3	13.6	3	23.1	0	....	1	50.0	1	14.3
1/800	0	....	1	3.0	2	9.1	1	7.7	4	30.1	0	....	2	28.6
1/400	1	4.0	4	12.1	2	9.5	0	....	2	15.4	0	....	0	....
1/200	6	24.0	3	9.1	0	....	1	7.7	0	....	0	....	0	....
1/100	2	8.0	2	6.1	0	....	0	....	0	....	0	....	0	....
1/50	0	....	1	3.0	0	....	0	....	0	....	0	....	0	....
< 1/50	2	8.0	1	3.0	3	13.6	2	15.4	4	30.1	0	....	2	28.6
Total	25	100.0	33	100.4	22	100.2	13	100.0	13	98.6	2	100.0	7	100.1
Total < 1/400	10	40.0	7	21.2	3	13.6	2	23.1	4	30.1	0	....	2	28.6

* At the end of 13 months a secondary injection, 10,000,000,000 phase I H. pertussis organisms, was given.

also summarized in chart 4, and values at three and 13 months after immunization are shown in table 18. In this older group preimmunization antibody did not influence the immediate responses, and its influence on the persistence of protective antibody levels was less marked than in the younger group. Another apparent difference was that among children with antibody prior to immunization there were fewer who did not have antibody at three months after immunization.

From chart 4 one can perceive that in the response following secondary immunization there was in both age groups a consistent difference favoring children without preimmunization antibody. These numbers are too small to attribute

significance to the observations, but they are highly suggestive that passive immunity in all age groups has an inimical effect on the establishment of good primary immunity to pertussis.

TABLE 18.—*H. Pertussis Agglutinins at Three and Thirteen Months After Vaccination Among Children Older than 3 Months Prior to Immunization and According to Their Preimmunization Status*

	Preimmunization Agglutinin Titers							
	3 Months After Immunization				13 Months After Immunization			
	< 1/50		> 1/50		< 1/50		> 1/50	
Agglutinin Titers	No.	%	No.	%	No.	%	No.	%
1/3,200	56	49.1	15	45.4	27	44.2	3	23.1
1/1,600	11	9.6	6	18.2	4	6.6	0	....
1/800	15	13.2	1	3.0	10	16.4	4	30.8
1/400	6	5.3	4	12.1	3	4.9	2	15.4
1/200	11	9.6	3	9.1	3	4.9	0	....
1/100	1	0.9	2	6.1	0	....	0	....
1/50	1	0.9	1	3.0	1	1.6	0	....
< 1/50	13	11.4	1	3.0	13	21.3	4	30.8
Total	114	100.0	33	99.9	61	99.9	13	100.0
Total < 1/400	26	22.8	5	21.2	17	27.8	4	30.8

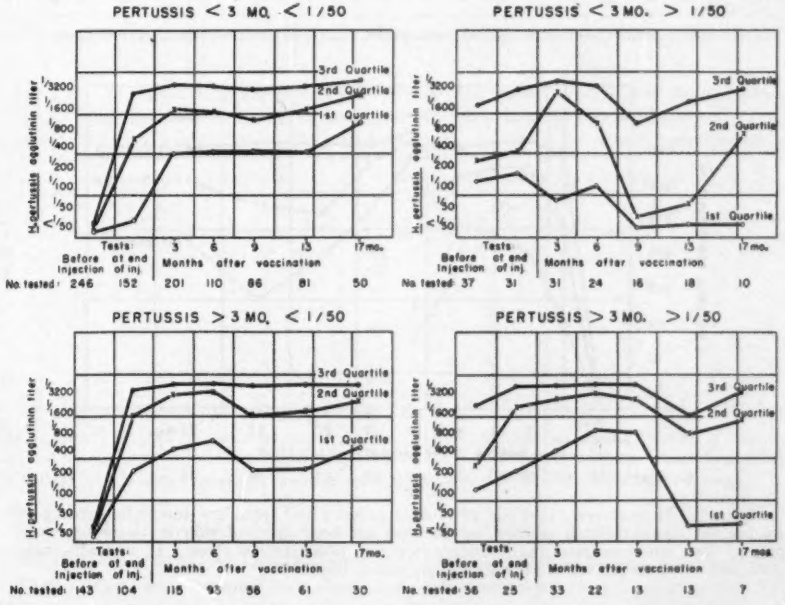
PERTUSSIS < 3 MO. < 1/50
PERTUSSIS < 3 MO. > 1/50
PERTUSSIS > 3 MO. < 1/50
PERTUSSIS > 3 MO. > 1/50
H. pertussis agglutinin titer
3rd Quartile
2nd Quartile
1st Quartile
Tests: Before injection / at end of inj. / Months after vaccination / 17 mo.
No. tested: 246 152 201 110 86 81 50
No. tested: 37 31 31 24 16 18 10
No. tested: 143 104 115 95 56 61 30
No. tested: 36 25 33 22 13 13 7

Chart 4.—H. pertussis agglutinin titers following primary vaccination among infants and children younger and older than 3 months without and with preimmunization antibody.

In table 19 and chart 5 are shown the responses of 147 infants and children selected because we had observed them after they received the booster immunizations without the loading due to the inclusion of many subjects on whom observa-

tions were limited to the early phases of the study. From this table it is apparent that there were about as many who failed to respond to the booster immunizations as who failed to respond to the primary vaccination, indicating the failure to establish in them a sound basic immunity. The persistence of antibody titers after secondary immunization was for the group as a whole on a level superior to that observed

TABLE 19.—*H. Pertussis Agglutinin Titers After Primary and Secondary Vaccination Among 147 Infants and Young Children Selected Because They Were Observed After the Secondary Vaccination*

Agglutinin Titers	Test: Before Injection		Test: At End of Injection		Months After Primary Immunization: 3		6		9		13*		13¼		17		21		27		33	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
1/3,200	5	4.0	27	25.2	53	45.3	41	44.1	33	33.0	36	32.1	18	78.2	44	37.9	9	37.5	10	41.6	9	34.6
1/1,600	1	0.8	15	14.0	19	16.2	15	16.1	21	21.0	16	14.3	2	8.7	31	26.7	1	4.2	1	4.2	6	23.1
1/800	1	0.8	11	10.3	9	7.7	13	14.0	11	11.0	13	11.6	0	....	14	12.1	5	20.8	3	12.5	3	11.5
1/400	4	3.2	9	8.4	7	6.0	7	7.5	9	9.0	8	7.1	0	....	7	6.0	4	16.7	2	8.3	3	11.5
1/200	5	4.0	14	13.1	11	9.4	4	4.3	6	6.0	11	9.8	0	....	3	2.6	1	4.2	2	8.3	1	3.8
1/100	1	0.8	7	6.5	4	3.4	2	2.1	0	....	0	....	0	....	1	0.9	0	....	1	4.2	0	....
1/50	4	3.2	2	1.9	0	....	0	....	0	....	2	1.8	0	....	0	....	0	....	0	....	0	....
< 1/50	105	83.3	22	20.6	14	12.0	11	11.8	20	20.0	26	23.2	3	13.0	16	13.8	4	16.7	5	20.8	4	15.4
Total	126	100.1	107	100.0	117	100.0	93	99.9	100	100.0	112	99.9	23	99.9	116	100.0	24	100.1	24	99.9	26	99.9
Total < 1/400	115	94.3	45	42.1	29	24.8	17	18.2	26	26.0	39	34.8	3	13.0	20	17.3	5	20.9	8	33.3	5	19.2

* At the end of 13 months a secondary injection, 10,000,000,000 phase I H. pertussis organisms, was given.

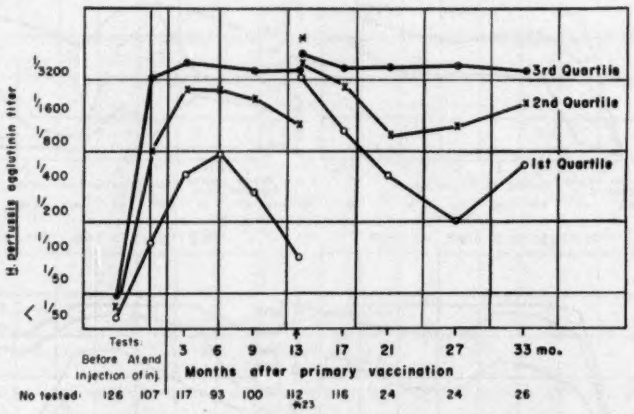

Chart 5.—H. pertussis agglutinin titers after primary and secondary vaccination among 147 infants and young children selected because they had been observed after the secondary vaccination. The arrow indicates the secondary injection, 10,000,000,000 phase I H. pertussis organisms, and the asterisk, one week after the secondary injection.

after primary immunization, though there were throughout 15 to 20 per cent of the children who showed titers of less than 1 : 50.

In an effort to establish the reasons for the failure of some of the children to develop higher titers, we have tabulated in table 20 the other titers observed at the various times on 66 infants and children who showed titers of less than 1 : 50 at

three months after the primary injection. While these children did show a scattering of relatively high titers at other periods, the majority of them were consistently nonresponders. We can offer no explanation for the variability observed except to attribute part of it to errors inherent in the technical procedures and to postulate that there may be some fluctuation in antibody levels from time to time, fluctuations which are not attributable to specific antigenic stimuli.

TABLE 20.—*H. Pertussis Agglutinins Among 66 Infants and Young Children Who Showed Titers of Less than 1: 50 Three Months After the Primary Immunization*

Agglutinin Titers	Test: Before Injection No.	%	Test: At End of Injection No.	%	Months After Primary Immunization: 3 No.	%	6 No.	%	9 No.	%	13* No.	%	13¾ No.	%	17 No.	%	27 No.	%	33 No.	%
1/3,200	0	....	1	2.5	0	....	1	3.3	1	5.5	1	4.6	0	....	2	15.4	0	....	0	....
1/1,600	0	....	1	2.5	0	....	2	6.6	2	11.2	4	18.1	0	....	1	7.7	0	....	0	....
1/800	1	2.0	2	5.1	0	....	2	6.7	1	5.5	2	9.1	0	....	2	15.4	0	....	0	....
1/400	1	2.0	2	5.1	0	....	2	6.6	0	....	1	4.5	0	....	2	15.4	0	....	0	....
1/200	4	8.2	3	7.7	0	....	2	6.6	0	....	1	4.5	0	....	1	7.7	1	100.0	0	....
1/100	1	2.0	1	2.6	0	....	1	3.4	1	5.5	0	....	0	....	0	....	0	....	0	....
1/50	1	2.0	1	2.5	0	....	0	....	0	....	0	....	0	....	0	....	0	....	0	....
< 1/50	41	83.7	28	71.8	66	100.0	20	66.6	13	72.2	13	59.1	1	100.0	5	38.4	0	....	2	100.0
Total	49	99.9	39	99.8	66	100.0	30	99.8	18	99.9	22	99.9	1	100.0	13	100.0	1	100.0	2	100.0
Total < 1/400	47	95.9	33	84.6	66	100.0	23	76.6	14	77.7	14	63.6	1	100.0	6	46.1	1	100.0	2	100.0

* At the end of 13 months a secondary injection, 10,000,000,000 phase I H. pertussis organisms, was given.

TABLE 21.—*H. Pertussis Agglutinins Among 16 Infants and Young Children Who Showed Titers of Less than 1: 50 Four Months After the First Secondary Immunization*

Agglutinin Titers	Test: Before Injection No.	%	Test: At End of Injection No.	%	Months After Primary Immunization: 3 No.	%	6 No.	%	9 No.	%	13* No.	%	13¾ No.	%	17 No.	%	21 No.	%	27 No.	%	33 No.	%
1/3,200	1	7.1	1	7.1	5	33.3	3	25.0	2	18.1	2	20.0	1	50.0	0	....	1	50.0	1	50.0	1	33.3
1/1,600	1	7.2	1	7.1	3	20.0	2	16.6	3	27.3	0	....	0	....	0	....	0	....	0	....	0	....
1/800	0	...	2	14.3	1	6.6	1	8.4	1	9.1	1	10.0	0	....	0	....	0	....	0	....	0	....
1/400	1	7.1	2	14.3	0	....	1	8.4	0	....	0	....	0	....	0	....	0	....	0	....	1	33.3
1/200	2	14.3	6	42.9	1	6.6	0	....	1	9.0	2	20.0	0	....	0	....	0	....	0	....	0	....
1/100	0	...	0	....	0	....	0	....	0	....	0	....	0	....	0	....	0	....	0	....	0	....
1/50	1	7.1	0	....	0	....	0	....	0	....	0	....	0	....	0	....	0	....	0	....	0	....
< 1/50	8	57.1	2	14.3	5	33.3	5	41.6	4	36.4	5	50.0	1	50.0	16	100.0	1	50.0	1	50.0	1	33.3
Total	14	99.9	14	100.0	15	99.8	12	100.0	11	99.9	10	100.0	2	100.0	16	100.0	2	100.0	2	100.0	3	99.9
Total < 1/400	11	78.5	8	57.2	6	39.9	5	41.6	5	45.4	7	70.0	1	50.0	16	100.0	1	50.0	1	50.0	1	33.3

* At the end of 13 months a secondary injection, 10,000,000,000 phase I H. pertussis organisms, was given.

In table 21 we have similarly shown the observations made on the 16 infants and children who showed titers of less than 1 : 50 after the secondary immunization. The numbers here became very small, but it is interesting to note that a high per cent of these children had preimmunization antibody. This was not true among the groups that failed to respond to the primary immunization, among which the percentage of children with preimmunization antibody was the same as observed for the whole study.

CONCLUSIONS FOR SECTIONS I THROUGH IV

1. Three injections of pertussis vaccine containing 80,000,000,000 phase I H. pertussis organisms adsorbed on aluminum hydroxide given over a period of three months produce a protective level of immunity in 77 per cent and some degree of immunity, as measured by agglutinin antibody, in 86 per cent of young infants and children.

2. The responses of the group younger than 3 months, particularly with regard to the maintenance of antibody levels, were modified considerably by the presence of passive immunity. In the groups older than 3 months, this effect was less noticeable.

3. Passive immunity not only interferes with the development and maintenance of high agglutinin titers but also tends to inhibit the development of a capacity to respond to secondary immunization.

4. Eighty billion phase I H. pertussis organisms adsorbed on aluminum hydroxide are not adequate to produce an optimum immunity in any age group.

5. There is a need for the improvement of pertussis vaccines which will allow an increase in the antigen content with a concomitant decrease in toxic reactions.

6. Toxic reactions to pertussis vaccination are not increased when the vaccinations are carried out in the younger infants.

7. (*a*) Pertussis vaccination in early infancy is essential if the mortality from the disease is to be greatly modified. (*b*) The administration of vaccine to pregnant women to enhance passive immunity would serve to complicate greatly the whole immunization program.

IMMUNIZATION IN THE YOUNG INFANT

Response to Combined Vaccines: V

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V. RESPONSES TO DIPHTHERIA IMMUNIZATION

THE FACT that young infants could be successfully immunized against pertussis,[1] the introduction of combined vaccines[2] which greatly reduce the difficulties of establishing an adequate immunization program by reducing the number of visits necessary, the incidental desirable lessening of the psychic trauma of "shots" when they are given very early in life and other factors stimulated our desire to inquire into the responses of young infants to diphtheria toxoid as used in modern vaccine preparations.

We have already mentioned[3] that the earlier studies are generally inadequate because they were carried out principally with toxin-antitoxin mixtures, but it may also be added that the early toxoids did not compare well with the present day preparations. Also, in many of the studies the reversal of the Schick reaction served as the only index of response.

Barr and Glenny[4] several years ago pointed out the need for using large doses of toxoid to establish primary immunity. They suggested using 100 Lf units of toxoid if a tolerable preparation could be obtained. To date, this suggestion has not been acted on, though the antigenic contents of some commercial toxoids have been increased.

The vaccine which we used,[5] containing 30 + Lf units of toxoid per milliliter, is superior in this respect to many of the toxoids available, though it is not comparable to some preparations used by Jensen.[6] We were therefore confident that some response would occur and that we would probably be able to establish primary immunity with some degree of anamnestic capacity.

From the Department of Pediatrics, Vanderbilt University School of Medicine.

1. Keller, A. E., Peterson, J. C., and Densen, P. M.: Opsonocytophagic Reactions to Whooping Cough Vaccination, Am. J. Pub. Health **32**:240-250 (March) 1942.

2. Ramon, G.: Mixed Vaccinations, Internat. Clin. **1**:241-255 (March) 1939.

3. Peterson, J. C., and Christie, A.: Immunization in the Young Infant: Response to Combined Vaccines, I.-IV., A. M. A. Am. J. Dis. Child. **81**:483-500 (April) 1951. (This article constitutes the first of the series.)

4. Barr, M., and Glenny, A. T.: Some Practical Applications of Immunological Principles, J. Hyg. **44**:135-142 (April) 1945.

5. The vaccine used in these studies was supplied by Cutter Laboratories, Berkeley, Calif.

6. Jensen, C.: Antitoxin Curve in Children After Active Immunization with Diphtheria Anatoxin, Acta path. et microbiol. Scandinav. **10**:137-158 (Nov.) 1933.

While most investigators,[7] relying primarily on Schick test results, were inclined to dismiss the possibility of diphtheria immunization in early infancy, the studies of Jakobkiewicz [8] indicated that the ability to respond to diphtheria toxoid was a progressive reaction rather than one showing an abrupt maturation with increasing age.

In the preceding paper [3] we discussed at some length the materials, procedures and reactions pertinent to this study.

In recapitulation, it seems adequate to state that the diphtheria immunization procedure consisted in two equal injections of aluminum hydroxide-adsorbed toxoid [5] in combination with tetanus toxoid, pertussis vaccine and typhoid vaccine given at an interval of three months. The total antigenic value of this material as regards diphtheria was between 70 and 80 Lf units and varied some with the different lots of vaccine used. Antibody determinations were made before immunization, at the completion of immunization and thereafter at intervals of three to four months. Determinations were also made just before and after a secondary immunization

TABLE 1.—*Diphtheria Antitoxin Levels Following Immunization Among 573 Infants and Young Children*

Antitoxin Titers	Test: Before Injection No.	Test: Before Injection %	Test: At End of Injection No.	Test: At End of Injection %	Months After Primary Immunization: 3 No.	3 %	6 No.	6 %	9 No.	9 %	13* No.	13* %	13¼ No.	13¼ %	17 No.	17 %	21 No.	21 %	27 No.	27 %	33 No.	33 %
1.0	31	6.7	32	8.9	78	17.4	31	11.1	17	8.5	14	6.7	16	69.6	40	34.8	6	26.1	4	15.4	4	16.7
0.1	84	18.3	69	19.2	140	31.2	70	25.0	51	25.6	39	18.7	4	17.4	32	27.8	10	43.5	12	46.2	10	41.7
0.03	108	23.5	92	25.6	90	20.1	67	23.9	44	22.1	55	26.3	..	....	25	21.7	2	8.7	8	30.8	8	33.3
0.01	42	9.1	27	7.5	30	6.7	31	11.1	20	10.1	23	11.0	1	4.3	5	4.3	3	13.0	1	3.8	2	8.3
0.003	2	0.4	..	....	24	5.4	19	6.8	9	4.5	19	9.1	..	....	7	6.1	2	8.7	..	....	..	....
< 0.003	193	42.0	139	38.7	86	19.2	62	22.1	58	29.1	59	28.2	2	8.7	6	5.2	..	....	1	3.8	..	....
Total	460	100.0	359	99.9	448	100.0	280	100.0	199	99.9	209	100.0	23	100.0	115	99.9	23	100.0	26	100.0	24	100.0
Total < 0.03	237	51.5	166	46.2	140	31.3	112	40.0	87	43.7	111	48.3	3	13.0	18	15.6	5	21.7	2	7.6	2	8.3

* At the end of 13 months a secondary injection, 15 Lf units of diphtheria toxoid, was given.

given 13 months after the completion of the primary immunization. Titrations were done by a modified Kellogg technic.

In the early part of our study the antitoxin titrations were not carried below 0.03 unit, as we had hoped to utilize Schick tests to show minimal values. However, this was impractical for a number of reasons peculiar to the study. Later titrations were carried as low as 0.003 unit, a value approximately equivalent to Schick reaction reversal.[9]

7. (*a*) Greengard, J., and Bernstein, H.: Passive Immunity in Infants and Their Response to Diphtheria, J. A. M. A. **105**:341-342 (Aug. 3) 1935. (*b*) Ribadeau-Dumas, L.; Loiseau, and Lacomme: La vaccination antidiphtérique des nourrissons, Bull. et mém. Soc. méd. d. hôp. de Paris **49**:1121-1123 (July 17) 1925. (*c*) Park, W. H., and Schroder, M. C.: Diphtheria Toxin-Antitoxin and Toxoid: A Comparison, Am. J. Pub. Health **22**:7-16 (Jan.) 1932. (*d*) Blum, J.: Age Factor in Active Immunization of Infants Against Diphtheria, J. A. M. A. **98**:1627-1629 (May 7) 1932.

8. Jakobkiewicz, J.: Immunization of Nurslings Against Diphtheria, Rev. d'immunol. **3**:70-78 (Jan.) 1937.

9. When there was an adequate number of determinations at levels of 0.01 and 0.003 unit, the determinations which terminated with less than 0.03 unit were distributed in the charts according to the findings among those titrated to the lower levels.

Immediate Responses.—The antitoxin titers following two injections of toxoid three months apart are shown in table 1, and the quartiles of the distribution are shown in chart 1. Three months after the second injection 80.8 per cent of the group had 0.003 unit or more of antitoxin and 17.4 per cent showed a level of 1 unit or more. In the following 10 months there was a gradual loss of immunity,

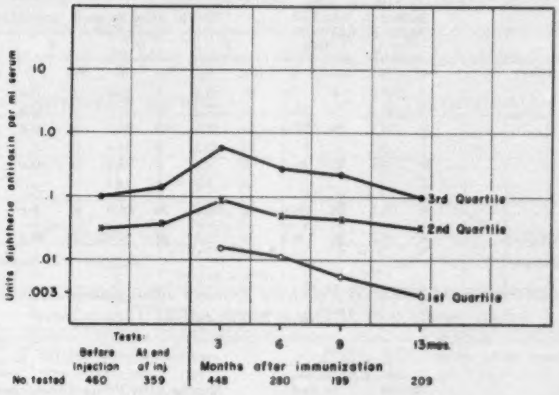

Chart 1.—Diphtheria antitoxin levels following primary immunization among 573 infants and young children, by quartiles. The positions of uncharted points are indeterminate because some serums were not titrated for < 0.03 unit.

TABLE 2.—*Diphtheria Antitoxin Levels Following Primary Immunization Among 352 Infants Aged Less Than 3 Months When Injections Were Initiated*

Antitoxin Titers	Test: Before Injection No.	%	Test: At End of Injection No.	%	Months After Primary Immunization: 3 No.	%	6 No.	%	9 No.	%	13 No.	%
1.0	24	8.5	9	4.3	21	7.7	8	4.9	5	4.3	4	3.3
0.1	71	25.2	30	14.5	76	27.7	37	22.8	29	25.0	16	13.2
0.03	73	25.9	58	28.0	62	22.6	36	22.2	24	20.7	31	25.6
0.01	..	....	..	....	30	10.9	32	19.8	18	15.5	19	15.7
0.003	114	40.4	110	53.1	32	11.7	22	13.6	12	10.3	14	11.6
< 0.003	..	....	..	....	53	19.3	27	16.7	28	24.1	37	30.6
Total	282	100.0	207	99.9	274	99.9	162	100.0	116	99.9	121	100.0
Total < 0.03	114	40.4	110	53.1	115	41.9	81	50.1	58	49.9	70	57.9

29 and 28 per cent showing titers less than 0.003 unit at nine and 13 months after immunization respectively. Only 8.5 and 6.7 per cent maintained levels of 1 unit or more at the same periods. From chart 1 it is apparent that the persistence of protection to a level of 0.01 unit was present for more than 60 per cent of the group. While these results are superior to those reported by Fraser and Halpern [10] or by

10. Fraser, D. T., and Halpern, K. C.: Anitoxic Response to Diphtheric Antigens, J. Immunol. **33**:323-335 (Oct.) 1937.

Greenberg and Fleming,[11] one cannot accept them as indicating a wholly satisfactory response.

TABLE 3.—*Diphtheria Antitoxin Levels Following Primary Immunizations Among 102 Infants Aged 3 to 5 Months at the Time Injections Were Initiated*

Antitoxin Titers	Test: Before Injection No.	Test: Before Injection %	Test: At End of Injection No.	Test: At End of Injection %	Months After Primary Immunization: 3 No.	3 %	6 No.	6 %	9 No.	9 %	13 No.	13 %
1.0	2	2.3	5	7.6	18	22.5	8	13.6	2	5.4	4	8.2
0.1	9	10.5	9	13.6	30	37.5	13	22.0	7	18.9	11	22.4
0.03	25	29.1	20	30.3	18	22.5	16	27.1	10	27.0	12	24.5
0.01	..	....	..	....	10	12.5	8	14.4	..	....	6	12.2
0.003	50	58.1	32	48.5	2	2.5	5	8.5	18	48.6	6	12.2
< 0.003	..	....	..	....	2	2.5	8	14.4	..	....	10	20.4
Total	86	100.0	66	100.0	80	100.0	59	100.0	37	99.9	49	99.9
Total < 0.03	50	58.1	32	48.5	14	17.5	22	37.3	18	48.6	22	44.8

TABLE 4.—*Diphtheria Antitoxin Levels Following Primary Immunization Among Fifty-Three Infants Aged 6 to 11 Months When Injections Were Initiated*

Antitoxin Titers	Test: Before Injection No.	Test: Before Injection %	Test: At End of Injection No.	Test: At End of Injection %	Months After Primary Immunization: 3 No.	3 %	6 No.	6 %	9 No.	9 %	13 No.	13 %
1.0	0	....	6	15.8	16	37.2	4	15.4	2	11.8	2	12.5
0.1	1	2.5	11	28.9	16	37.2	8	30.8	4	23.5	5	31.25
0.03	7	17.5	10	26.3	7	16.3	10	38.5	5	29.4	5	31.25
0.01	..	....	..	....	..	....	..	....	..	....	..	....
0.003	32	80.0	11	28.9	4	9.3	4	15.4	6	35.3	4	25.0
< 0.003	..	....	..	....	..	....	..	....	..	....	..	....
Total	40	100.0	38	99.9	43	100.0	26	100.1	17	100.0	16	100.0
Total < 0.03	32	80.0	11	28.9	4	9.3	4	15.4	6	35.3	4	25.0

TABLE 5.—*Diphtheria Antitoxin Levels Observed Following Primary Immunization Among Sixty-Six Children Aged More Than 12 Months When Injections Were Initiated*

Antitoxin Titers	Test: Before Injection No.	Test: Before Injection %	Test: At End of Injection No.	Test: At End of Injection %	Months After Primary Immunization: 3 No.	3 %	6 No.	6 %	9 No.	9 %	13 No.	13 %
1.0	3	5.8	11	22.9	22	43.1	11	33.3	6	20.7	2	10.0
0.1	3	5.8	18	37.5	18	35.3	11	33.3	12	41.4	7	35.0
0.03	5	9.6	6	12.5	4	7.8	6	18.2	7	24.1	6	30.0
0.01	..	....	..	....	..	....	..	....	..	....	..	....
0.003	41	78.8	13	27.1	7	13.7	5	15.2	4	13.8	5	25.0
< 0.003	..	....	..	....	..	....	..	....	..	....	..	....
Total	52	100.0	48	100.0	51	99.9	33	100.0	29	100.0	20	100.0
Total < 0.03	41	78.8	13	27.1	7	13.7	5	15.2	4	13.8	5	25.0

Effect of Age on Antitoxin Response.—The diphtheria antitoxin values according to the age group are shown in tables 2, 3, 4 and 5 and are summarized in chart

11. Greenberg, L., and Fleming, D. S.: Immunizing Efficiency of Diphtheria Toxoid When Combined with Various Antigens, Canad. J. Pub. Health **39**:131-135 (April) 1948.

2. As can be readily appreciated from the chart, there is a slight improvement with each increasing age group of the general pattern of the distribution curves. This is most striking if one compares the lower quartiles of the youngest age group with those of the oldest age group. However, 80.7 per cent of those less than 3 months of age showed more than 0.003 unit three months after injections were completed and 7.7 per cent showed levels of 1 unit or more. In the 6 to 11 month group 37 per cent showed levels of 1 unit or more, and in the group of more than a year 43 per cent showed such high levels. The antitoxin values observed in the various age groups three months after immunization are shown in table 6.

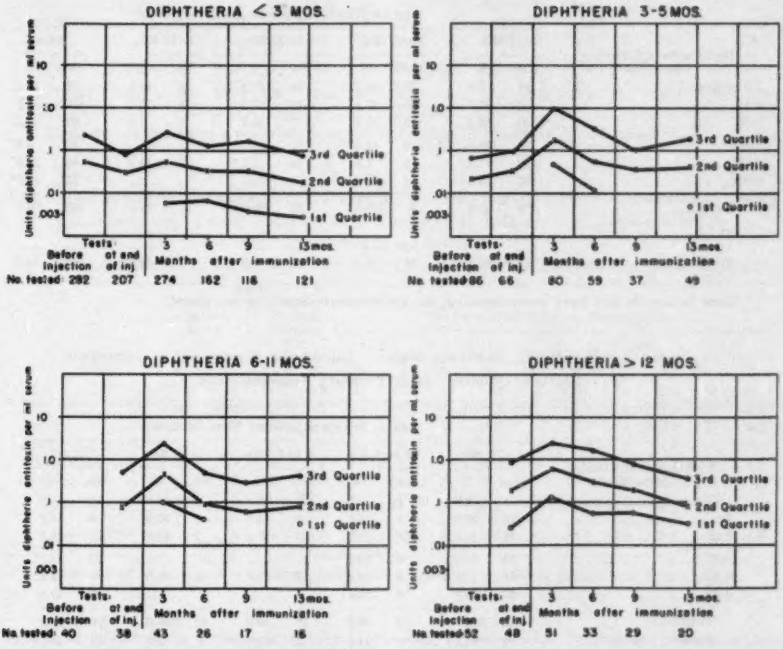

Chart 2.—Diphtheria antitoxin levels following primary immunization among the various age groups, by quartiles. The positions of the uncharted points are indeterminate because some serums were not titrated for < 0.03 unit.

In table 6 it is clearly apparent that each age increase is associated with an improvement in the number of children showing high levels. This would probably be even more striking had the logarithmic progression to 3 unit and 10 unit titrations been completed.

Not less significant is the fact that the age groups vary in their ability to maintain the response. These differences are apparent in tables 2, 3, 4 and 5 but can be better visualized in table 7, which shows the values observed for the various age groups 13 months after completion of primary immunization.

From table 7 it is apparent that while 75 per cent of the two oldest age groups maintained fairly high levels of antitoxic immunity for 13 months after injection, only 42.1 per cent of the youngest group maintained high levels for this long.

From the foregoing it appears that age when considered without relation to other factors does modify the response to diphtheria toxoid injections, as the youngest groups showed a greater proportion of children who failed to achieve moderately high and high levels of antitoxin.

Effect of Passive Immunity.—The fact that passive immunity alters the response to diphtheria has been known since Greenberg and Fleming's studies [11] and has

TABLE 6.—*Diphtheria Antitoxin Values Among the Various Age Groups Three Months After Primary Immunization*

Diphtheria Antitoxin, Units/Ml.	Age at Which Injections Were Initiated									
	< 3 Mo.		3 to 5 Mo.		6 to 11 Mo.		> 12 Mo.		Total	
	No.	%	No.	%	No.	%	No.	%	No.	%
1.0 or more	21	7.7	18	22.5	16	37.2	22	43.1	77	17.2
0.1	76	27.7	30	37.5	16	37.2	18	35.3	140	31.2
0.03	62	22.6	18	22.5	7	16.3	4	7.8	91	20.3
0.01	30	10.9	10	12.5	..	....	..	....	40	8.9*
0.003	32	11.7	2	2.5	4	9.3	7	13.7	45	10.0*
< 0.003	53	19.3	2	2.5	..	....	..	....	55	12.3*
Total	274	99.9	80	100.0	43	100.0	51	99.9	448	99.9
Total < 0.03	115	42.0	14	17.5	4	9.3	7	13.7	140	31.2

* These figures do not have exact meaning, as distributions cannot be completed.

TABLE 7.—*Diphtheria Antitoxin Values Among the Various Age Groups Thirteen Months After Primary Immunization*

Diphtheria Antitoxin, Units/Ml.	Age at Which Injections Were Initiated									
	< 3 Mo.		3 to 5 Mo.		6 to 11 Mo.		> 12 Mo.		Total	
	No.	%	No.	%	No.	%	No.	%	No.	%
1.0 or more	4	3.3	4	8.2	2	12.5	2	10.0	12	5.8
0.1	16	13.2	11	22.4	5	31.2	7	30.0	39	18.9
0.03	31	25.6	12	24.5	5	31.2	6	35.0	54	26.2
0.01	19	15.7	6	12.2	..	....	..	....	25	12.1*
0.003	14	11.6	6	12.2	4	25.0	5	25.0	29	14.1*
< 0.003	37	30.6	10	20.4	..	....	..	....	47	22.8*
Total	121	100.0	49	99.9	16	99.9	20	100.0	206	99.9
Total < 0.03	70	57.9	22	44.9	4	25.0	5	25.0	101	49.0

* These figures do not have exact meaning, as the distribution cannot be completed.

been reemphasized by Cooke,[12] di Sant'Agnese [13] and Vahlquist and others.[14] Our series gave us an opportunity to evaluate very carefully the effect of passive

12. Cooke, J. V.: Antibody Formation in Early Infancy Against Diphtheria and Tetanus Toxoids, J. Pediat. **33**:141-146 (Aug.) 1948.

13. di Sant'Agnese, P. A.: Combined Immunization Against Diphtheria, Tetanus and Pertussis in Newborn Infants: II. Duration of Antibody Levels; Antibody Titers After Booster Dose; Effect of Passive Immunity to Diphtheria on Active Immunization with Diphtheria Toxoid, Pediatrics **3**:181-194 (Feb.) 1949.

14. Vahlquist, B.; Murray, U., and Persson, N. G.: Studies on Diphtheria: Immunization Against Diphtheria in Newborn Babies and in Infants, Acta pædiat. **35**:130-148, 1948. Vahlquist, B., and Hackzell, G.: Studies on Diphtheria: Duration of Immunity Against Diphtheria, ibid. **35**:149-159, 1948.

TABLE 8.—*Diphtheria Antitoxin Levels Following Primary and Secondary Immunization Among 237 Infants and Young Children Who Had Less Than 0.03 Unit of Antitoxin When the Injections Were Initiated*

Antitoxin Titers	Test: Before Injection No.	Test: Before Injection %	Test: At End of Injection No.	Test: At End of Injection %	Months After Primary Immunization: 3 No.	3 %	6 No.	6 %	9 No.	9 %	13* No.	13* %	17 No.	17 %
1.0	..	....	19	11.9	47	26.3	19	16.0	8	9.5	8	10.7	18	38.3
0.1	..	....	35	21.9	66	36.9	44	37.0	24	28.6	18	24.0	14	29.8
0.03	..	....	40	25.0	23	12.8	27	22.7	24	28.6	25	33.3	7	14.9
0.01	..	....	11	6.9	13	7.3	12	10.1	10	11.9	7	9.3	2	4.3
0.003	237	100.0	..	....	6	3.4	5	4.2	1	1.2	6	8.0	5	10.6
< 0.003	..	....	55	33.4	24	13.2	12	10.1	17	20.2	11	14.7	1	2.1
Total	237	100.0	160	100.1	179	100.1	119	100.1	84	100.0	75	100.0	47	100.0
Total < 0.03	237	100.0	66	40.3	43	24.1	29	24.4	28	33.3	24	32.0	8	17.0

* At the end of 13 months a secondary injection, 15 Lf units of diphtheria toxoid, was given.

TABLE 9.—*Diphtheria Antitoxin Levels Following Primary and Secondary Immunization Among 185 Infants and Young Children Who Had 0.03 to One Unit of Antitoxin When Injections Were Initiated*

Antitoxin Titers	Test: Before Injection No.	Test: Before Injection %	Test: At End of Injection No.	Test: At End of Injection %	Months After Primary Immunization: 3 No.	3 %	6 No.	6 %	9 No.	9 %	13* No.	13* %	17 No.	17 %
1.0	..	....	4	3.4	18	12.2	4	4.3	7	9.9	9	22.0	14	32.5
0.1	185	100.0	18	15.1	39	26.4	15	16.3	17	23.9	3	7.3	13	30.2
0.03	..	....	35	29.4	38	25.7	26	28.3	9	12.7	9	22.0	10	23.2
0.01	..	....	9	7.6	12	8.1	8	8.7	9	12.7	3	7.3	1	2.3
0.003	..	....	..	....	6	4.1	8	8.7	4	7.0	5	12.2	2	4.6
< 0.003	..	....	53	44.5	35	23.6	31	33.7	24	33.8	12	29.3	3	7.0
Total	185	100.0	119	100.0	148	100.1	92	100.0	71	100.1	41	100.1	43	99.8
Total < 0.03	..	....	62	52.1	53	35.8	47	41.1	38	53.5	20	48.8	7	13.9

* At the end of 13 months a secondary injection, 15 Lf units of diphtheria toxoid, was given.

TABLE 10.—*Diphtheria Antitoxin Levels Following Primary and Secondary Immunizations Among Thirty-Eight Infants and Children Who Had One Unit or More Antitoxin When Injections Were Initiated*

Antitoxin Titers	Test: Before Injection No.	Test: Before Injection %	Test: At End of Injection No.	Test: At End of Injection %	Months After Primary Immunization: 3 No.	3 %	6 No.	6 %	9 No.	9 %	13* No.	13* %	17 No.	17 %
1.0	38	100.0	4	14.3	3	10.0	3	17.6	..	....	..	....	..	....
0.1	..	....	4	14.3	5	16.7	2	11.8	..	....	1	7.7	1	25.0
0.03	..	....	9	32.1	9	30.0	4	23.5	3	33.3	1	7.7	..	....
0.01	..	....	2	7.1	..	....	4	23.5	..	....	1	7.7	..	....
0.003	..	....	..	....	2	6.7	2	11.8	..	....	2	15.4	1	25.0
< 0.003	..	....	9	32.1	11	36.7	2	11.8	6	66.7	8	61.5	2	50.0
Total	38	100.0	28	99.9	30	100.1	17	100.0	9	100.0	13	100.0	4	100.0
Total < 0.03	..	....	11	39.2	13	43.4	8	47.1	6	66.7	11	84.6	3	75.0

* At the end of 13 months a secondary injection, 15 Lf units of diphtheria toxoid, was given.

immunity. Of our patients, 48.5 per cent showed antibody levels of 0.03 unit or more when their immunizations were initiated. For the purpose of observing the effect of passive immunity, three groups were made: those patients with less than 0.03 unit when injections were started, those with 0.03 to 0.1 unit and those with 1 unit or more. The values for these groups are shown in tables 8, 9 and 10 and are summarized in chart 3. Also shown in the chart is the recall response following the injection of 0.5 milliliter of toxoid 13 months after primary immunization. It is apparent from this chart that passive immunity prior to immunization modified the response to primary immunization as much as or more than did the age of the patient. Considering the fact that many of those within the group having the least

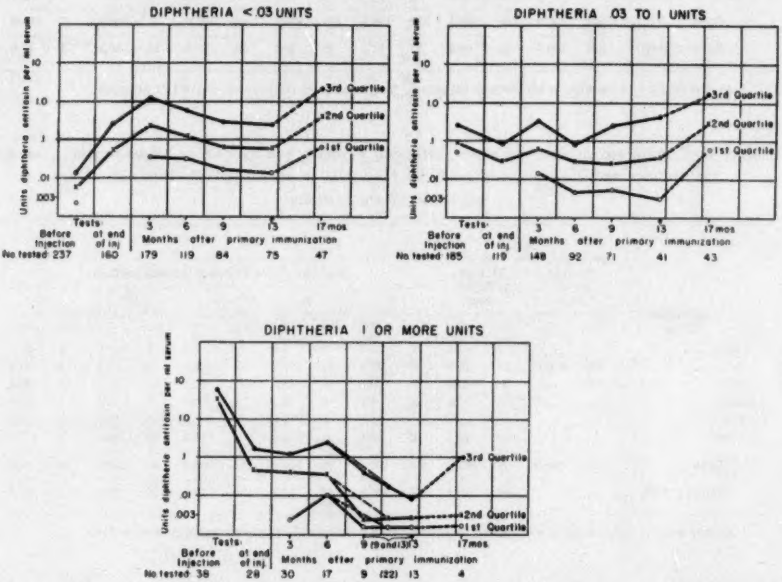

Chart 3.—Diphtheria antitoxin levels following primary and secondary immunizations among the groups according to their preimmunization antitoxin levels. The arrow indicates the secondary injection, 0.5 milliliter of diphtheria toxoid. The positions of uncharted points are indeterminate because some serums were not titrated for < 0.03 unit.

amount of antitoxin had some passive immunity, it is probable that the results would have been even more marked if the comparison level could have been lowered. As far as moderate degrees of passive immunity are concerned, they did not seem to modify the development of a capacity to respond to a booster injection, the post-injection responses being similar for those with less than 0.03 unit and those with 0.03 to 0.1 unit of passive immunity before the primary immunization. However, those with 1.0 or more units of passive immunity not only had a very poor response to primary immunization but also responded poorly after the secondary injection. The values observed after the booster injection for these three groups are shown in table 11.

While the number of infants with 1 unit or more of passive immunity tested after the secondary injection is very small, too small to be statistically significant, the differences observed are suggestive. Fortunately, the number of infants with this level of passive immunity is small, only 8.5 per cent, even among those aged less than 3 months. It should also be pointed out that three of the 31 with 1 unit or more came from the age group of more than 12 months, in which one might assume the immunity to be active rather than passive. The tabulations were not

TABLE 11.—*Diphtheria Antitoxin Values Observed Three Months After the First Secondary Immunization According to the Degree of Passive Immunity Present Before Primary Immunization*

Diphtheria Antitoxin, Units/Ml.	< 0.03 Unit		0.03 to 1 Unit		1 Unit or More	
	No.	%	No.	%	No.	%
1.0	18	38.3	14	32.5	..	....
0.1	14	29.8	13	30.2	..	....
0.03	7	14.9	10	23.2	1	25.0
0.01	2	4.3	1	2.3	..	....
0.003	5	10.6	2	4.6	1	25.0
< 0.003	1	2.1	3	7.0	2	50.0
Total	47	100.0	43	99.8	4	100.0
Total < 0.03	8	17.0	6	13.9	3	75.0

TABLE 12.—*Diphtheria Antitoxin Levels Following Primary and Secondary Immunization Among 114 Infants Aged Less Than 3 Months and Having Less Than 0.03 Unit of Antitoxin When Injections Were Initiated*

	Test				Months After Primary Immunization											
	Before Injection		At End of Injection		3		6		9		13*		13¼		17	
Antitoxin Titers	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
1.0	..	....	5	6.8	12	14.3	5	9.3	1	2.7	..	....	1	100.0	10	40.0
0.1	..	....	11	15.1	20	34.5	21	39.0	12	32.4	8	25.0	..	....	6	24.0
0.03	..	....	22	30.1	13	15.5	10	18.5	11	29.7	13	40.6	..	....	4	16.0
0.01	..	....	9	12.3	9	10.7	6	11.1	5	13.5	3	9.3	..	....	1	4.0
0.003	..	....	0	....	6	7.1	4	7.4	1	2.7	2	6.2	..	....	3	12.0
< 0.003	114	100.0	26	35.6	15	17.8	8	14.8	7	18.9	6	18.7	..	....	1	4.0
Total	114	100.0	73	99.9	84	99.9	54	100.1	37	99.9	32	99.8	1	100.0	25	100.0
Total < 0.03	114	100.0	9	47.9	30	35.6	18	33.3	13	35.1	11	34.2	..	....	5	20.0

* At the end of 13 months a secondary injection, 15 Lf units of diphtheria toxoid, was given.

corrected to delete the data from these patients, but it can be assumed that their presence does not have an adverse effect on the total data on the responses.

Effect of Age and Passive Immunity.—Inasmuch as immaturity and the presence of passive immunity are common to some groups, we have subdivided the groups to show the effect of passive immunity and immaturity independently. To maintain statistically significant groups, we have taken 3 months of age and 0.03 unit of antitoxin as the dividing points.

Tables 12, 13, 14 and 15 show the antitoxin values according to the preimmunization age and the level of passive immunity. The distribution quartiles for these tables are shown in chart 4, and in tables 16 and 17 are shown the comparative responses three months and 13 months after the immunizations.

TABLE 13.—*Diphtheria Antitoxin Levels Following Primary and Secondary Immunization Among 168 Infants Aged Less Than 3 Months Who Had More Than 0.03 Unit of Antitoxin When Injections Were Initiated*

	Test at End of Injection		Months After Primary Immunization															
			3		6		9		13*		13¼		17		21		27		33	
Antitoxin Titers	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
1.0	3	2.8	9	6.8	2	2.8	4	6.6	3	4.9	6	75.0	9	27.3	2	40.0	..	....	1	11.1
0.1	14	13.1	30	22.6	8	11.3	15	24.6	5	8.2	1	12.5	8	24.2	2	40.0	4	80.0	5	55.5
0.03	32	29.9	35	26.3	18	25.4	7	11.5	13	21.3	..	....	10	30.3	..	....	1	20.0	2	22.2
0.01	11	10.3	9	6.8	10	14.1	7	11.5	7	11.5	..	....	..	....	..	....	..	....	1	11.1
0.003	..	....	8	6.0	8	11.3	5	8.2	6	9.8	..	....	2	6.1	1	20.0	..	....	..	....
< 0.003	47	43.9	42	31.6	25	35.2	23	37.7	27	44.3	1	12.5	4	12.1	..	....	..	....	..	....
Total	107	100.0	133	100.0	71	100.1	61	100.1	61	100.0	8	100.0	33	100.0	5	100.0	5	100.0	9	99.9
Total < 0.03	58	54.2	59	44.4	43	60.6	35	57.4	39	65.6	1	12.5	6	18.2	1	20.0	..	....	1	11.1

* At the end of 13 months a secondary injection, 15 Lf units of diphtheria toxoid, was given.

TABLE 14.—*Diphtheria Antitoxin Levels Following Primary and Secondary Immunizations Among 123 Infants and Young Children Aged More Than 3 Months Who Had Less Than 0.03 Unit of Antitoxin When Injections Were Initiated*

	Test				Months After Primary Immunization									
	Before Injection		At End of Injection		3		6		9		13*		13¼		17	
Antitoxin Titers	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
1.0	..	....	13	14.9	35	36.8	13	20.0	6	12.8	7	16.3	4	57.1	8	36.4
0.1	..	....	24	27.6	36	37.9	23	35.4	12	25.5	11	25.6	2	28.6	8	36.4
0.03	..	....	19	21.8	11	11.6	18	27.7	14	29.8	12	27.9	..	....	3	13.6
0.01	..	....	2	2.3	4	4.2	6	9.2	5	10.6	4	9.3	1	14.2	1	4.5
0.003	123	100.0	0	....	0	....	1	1.5	0	....	4	9.3	..	....	2	9.1
< 0.003	..	....	29	33.3	9	9.5	4	6.1	10	21.3	5	11.6	..	....	..	....
Total	123	100.0	87	99.9	95	100.0	65	99.9	47	100.0	43	100.0	7	99.9	22	100.0
Total < 0.03	123	100.0	31	35.6	13	13.7	11	16.8	15	31.9	13	30.2	1	14.2	3	13.6

* At the end of 13 months a secondary injection, 15 Lf units of diphtheria toxoid, was given.

TABLE 15.—*Diphtheria Antitoxin Levels Following Primary and Secondary Immunizations Among Fifty-Five Infants and Young Children Aged More Than 3 Months and Having More Than 0.03 Unit of Antitoxin When Injections Were Initiated*

	Test				Months After Primary Immunization															
	Before Injection		At End of Injection		3		6		9		13*		13¼		17		21		27		33	
Antitoxin Titers	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
1.0	2	5.6	5	12.5	12	26.7	6	15.8	3	15.8	1	3.8	3	60.0	5	35.7	..	....	..	....	..	....
0.1	9	25.0	8	20.0	14	31.1	7	18.4	4	21.1	4	15.4	1	20.0	6	42.8	3	100.0	4	100.0	2	100.0
0.03	25	69.4	12	30.0	12	26.7	13	34.2	3	15.8	7	26.9	..	....	1	7.1	..	....	..	....	..	....
0.01	..	....	..	....	3	6.7	..	....	2	10.5	3	11.5	..	....	1	7.1	..	....	..	....	..	....
0.003	..	....	..	....	..	....	2	5.3	..	....	3	11.5	..	....	..	....	..	....	..	....	..	....
< 0.003	..	....	15	37.5	4	8.9	10	26.3	7	36.8	8	30.8	1	20.0	1	7.1	..	....	..	....	..	....
Total	36	100.0	40	100.0	45	100.1	48	100.0	19	100.0	26	99.9	5	100.0	14	99.8	3	100.0	4	100.0	2	100.0
Total < 0.03	0	0	15	37.5	7	15.6	12	31.6	9	47.3	14	53.8	1	20.0	2	14.2	0	....	0	....	0	....

* At the end of 13 months a secondary injection, 15 Lf units of diphtheria toxoid, was given.

In comparing the values for those without passive immunity younger and older than 3 months (table 16), we find that 17.8 per cent of the group less than 3 months and without passive immunity showed less than 0.003 unit three months after immunization, while 9.5 per cent of the older group showed a failure to respond; only 14.3 per cent of the younger group showed levels of 1 unit or more, while 36.8 per cent of the older group showed such a level.

In comparing the values for those with more than 0.03 unit of passive immunity, we find that 31.6 per cent of the younger group showed response levels of less than 0.003, while in the older group only 8.9 per cent showed this failure to respond. With regard to high levels of response, only 6.8 per cent of the younger group

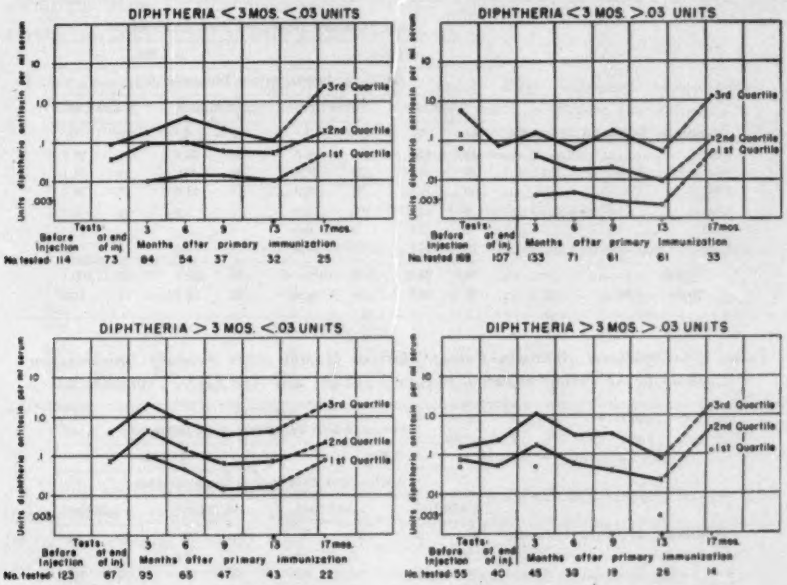

Chart 4.—Diphtheria antitoxin levels following primary and secondary immunizations among infants younger than and older than 3 months of age when their immunizations were initiated according to their preimmunization antitoxin levels. The arrow indicates the secondary injection, 0.5 milliliter diphtheria toxoid. The positions of uncharted points are indeterminate because some serums were not titrated for < 0.03 unit.

showed 1.0 unit or more, while in the older group this level was attained by 26.7 per cent.

From these results it appears that both passive immunity and age determine the failure of the young infant to respond well to diphtheria toxoid. In the older age group the passive immunity did not interfere with the ability to respond minimally, though there were more among the group without passive immunity who achieved high levels of antitoxin. This is probably also influenced by the fact that some of the group over 12 months of age with preimmunization immunity had active rather than passive immunity and therefore should have shown excellent responses.

One finds that preimmunization immunity influences greatly the ability of both the younger and the older age groups to maintain an immunity at minimal, protec-

tive or high levels (table 17). Thirty-one per cent of the older group and 44 per cent of the younger group with preimmunization antibody showed less than 0.003 unit of antitoxin 13 months after immunization, while only 12 and 19 per cent respectively of those without passive immunity had fallen to this level. Sixty-six per cent of the younger group and 54 per cent of the older group with passive immunity showed levels of less than 0.03 unit, while in the group without passive immunity the corresponding values were 34 and 30 per cent. In the older group there were more among those without passive immunity showing high levels at

TABLE 16.—*Diphtheria Antitoxin Values Three Months After Primary Immunization According to the Preimmunization Antitoxin Levels and Age*

	Age at Which Injections Were Initiated							
	<3 Mo.				>3 Mo.			
	Antitoxin Levels Before Immunization							
	<0.03 Unit		>0.03 Unit		<0.03 Unit		>0.03 Unit	
Diphtheria Antitoxin, Units/Ml.	No.	%	No.	%	No.	%	No.	%
1.0	12	14.3	9	6.8	35	36.8	12	26.7
0.1	29	34.5	30	22.6	36	37.9	14	31.1
0.03	13	15.5	35	26.3	11	11.6	12	26.7
0.01	9	10.7	9	6.8	4	4.2	3	6.7
0.003	6	7.1	8	6.0	0	....	..	....
<0.003	15	17.8	42	31.6	9	9.5	4	8.9
Total	84	99.9	133	100.1	95	100.0	45	100.1
Total <0.03	30	35.7	59	44.4	13	13.7	7	15.5

TABLE 17.—*Diphtheria Antitoxin Values Thirteen Months After Primary Immunization According to the Preimmunization Passive Immunity and Age Before Immunization*

	Age at Which Injections Were Initiated							
	<3 Mo.				>3 Mo.			
	Antitoxin Levels Before Immunization							
	<0.03 Unit		>0.03 Unit		<0.03 Unit		>0.03 Unit	
Diphtheria Antitoxin, Units/Ml.	No.	%	No.	%	No.	%	No.	%
1.0	0	....	3	4.9	7	16.3	1	3.8
0.1	8	25.0	5	8.2	11	25.6	4	15.4
0.03	13	40.6	13	21.3	12	27.9	7	26.9
0.01	3	9.3	7	11.5	4	9.3	3	11.5
0.003	2	6.2	6	9.8	4	9.3	3	11.5
<0.003	6	18.7	27	44.3	5	11.6	8	30.8
Total	32	99.8	61	100.0	43	100.0	26	99.9
Total <0.03	11	34.4	40	65.6	13	30.2	14	53.8

13 months than among those who had passive immunity. In the younger group, probably as a result of freak distribution with small numbers, there were none without passive immunity who maintained high levels of antitoxin for 13 months, while there were three among those with passive immunity who did maintain 1 unit or more. In general, it seemed that passive immunity was more important than age in determining whether immunity would be carried through the first 13 months after vaccination, both in the younger age group and in those older, but age was also of some importance, as the older group contained fewer children whose protection had lapsed.

Effect of Age and Passive Immunity on Secondary Immunization.—While it is of great interest to see how young infants respond and maintain their immunity, it is probably more important to observe how well their basic immunity is established with respect to their capacity to respond to recall or secondary immunization. The need for reimmunization in diphtheria control is well recognized.[15]

Though it has been shown that very small stimuli will serve for recall diphtheria immunizations,[16] we used in this study relatively large amounts of toxoid because it is desirable to utilize relatively large doses of pertussis vaccine for recall [17] and the amount of diphtheria toxoid used was determined by the pertussis needs.

In this connection, it might be better to have a special vaccine mixture for use in recall injections. The number showing reactions to these recall injections was about the same as that encountered for the primary injections, but moderately severe reactions occurred with greater frequency.

TABLE 18.—*Diphtheria Antitoxin Values Four Months After Secondary Immunization According to Preimmunization Passive Immunity and Age Before Immunization*

	Age at Which Injections Were Initiated											
	< 3 Mo.						> 3 Mo.					
	Antitoxin Levels Before Immunization											
Diphtheria Antitoxin, Units/Ml.	< 0.03 Unit		> 0.03 Unit		Total < 3 Mo.		< 0.03 Unit		> 0.03 Unit		Total > 3 Mo.	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
1.0	10	40.0	9	27.3	19	32.8	8	36.4	5	35.7	13	36.1
0.1	6	24.0	8	24.2	14	24.1	8	36.4	6	42.8	14	39.0
0.03	4*	16.0	10	30.3	14	24.1	3	13.6	1	7.1	4	11.1
0.01	1	4.0	0	0.0	1	1.7	1	4.5	1	7.1	2	5.5
0.003	3	12.0	2	6.1	5	8.6	2	9.1	0	0.0	2	5.5
< 0.003	1	4.0	4	12.1	5	8.6	0	0.0	1	7.1	1	2.8
Total	25	100.0	33	100.0	58	99.9	22	100.0	14	99.8	36	100.0
Total < 0.03	5	20.0	6	18.2	11	19.0	3	13.6	2	14.3	5	13.9

While the responses following secondary immunization are shown in the preceding tables and in chart 3, they are again summarized for comparison in table 18. In the comparison of those with and without passive immunity, it appears that in the group under 3 months of age those who had moderate passive immunity failed to respond more frequently than did those without passive immunity. In the older group the only infant failing to respond to secondary injection was one with preimmunization passive immunity. Also, there was among the younger group a slight relative failure of those with preimmunization passive immunity to attain high levels after the recall immunization, while in this respect the young infants without passive immunity responded as well as those in the older group. None of these differences are statistically significant, and, generally speaking, the responses following secondary immunization are quite satisfactory for all groups, though they are quite inferior to those observed in tetanus immunization.

15. Wishart, F. O., and Reid, M. R.: A Study of Diphtheria Antitoxin Response to Recall Doses of Specific Antigen, Canad. J. Pub. Health **38**:131-140 (March) 1947.

16. Glenny, A. T., and Allen, K.: The Schick Dose of Diphtheria Toxin as a Secondary Stimulus, J. Hyg. **21**:104-111 (June) 1922.

17. Sako, W.; Trueting, W. L.; Witt, D. B., and Nichamin, S. J.: Early Immunization Against Pertussis with Alum Precipitated Vaccine, J. A. M. A. **127**:379-384 (Feb.) 1945.

TABLE 19.—*Diphtheria Antitoxin Levels Following Primary and Recall Immunizations Among 145 Infants and Young Children Selected Because They Were Observed After the Booster Injection*

Antitoxin Titers	Test: Before Injection No.	%	Test: At End of Injection No.	%	Months After Primary Immunization: 3 No.	%	6 No.	%	9 No.	%	13* No.	%	13¼ No.	%	17 No.	%	21 No.	%	27 No.	%	33 No.	%
1.0	3	2.5	4	3.8	22	19.6	12	13.6	9	9.3	9	8.4	16	69.6	40	34.8	6	26.1	4	15.4	4	16.7
0.1	24	19.7	23	22.1	35	31.2	25	28.4	22	22.7	19	17.8	4	17.4	32	27.8	10	43.5	12	46.2	10	41.7
0.03	34	27.9	26	25.0	23	20.5	25	28.4	25	25.8	30	28.0	..	....	25	21.7	2	8.7	8	30.8	8	33.3
0.01	8	6.6	9	8.7	4	3.6	8	9.1	14	14.4	12	11.2	1	4.3	5	4.3	3	13.0	1	3.8	2	8.3
0.003	..	....	..	....	4	3.6	4	4.5	3	3.1	9	8.4	..	....	7	6.1	2	8.7	..	....	..	....
< 0.003	54	43.4	42	40.4	24	21.4	14	15.9	24	24.7	28	26.2	2	8.7	6	5.2	..	....	1	3.8	..	....
Total	122	100.1	104	100.0	112	99.9	88	99.9	97	100.0	107	100.0	23	100.0	115	99.9	23	100.0	26	100.0	24	100.0
Total < 0.03	95	50.0	51	49.1	32	28.6	26	29.5	41	42.2	49	45.8	3	13.0	18	16.6	5	21.7	2	7.6	2	8.3

* At the end of 13 months a secondary injection, 15 Lf units of diphtheria toxoid, was given.

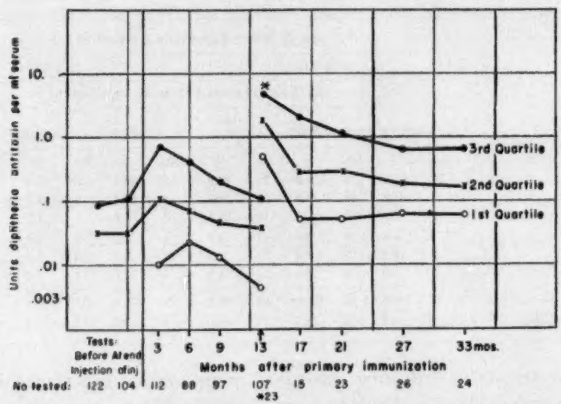

Chart 5.—Diphtheria antitoxin levels following primary and secondary immunizations among 145 infants and children selected because they had been observed after the secondary immunization. The arrow indicates the secondary injection, 0.5 milliliter of diphtheria toxoid, and the asterisk, one week after the secondary injection. The positions of uncharted points are indeterminate because some serums were not titrated for < 0.03 unit.

Persistence of Immunity After Secondary Stimulus.—In table 19 are shown the antitoxin values of 145 infants and young children selected from the larger group because we had observed them after the secondary immunization. From this table one can visualize the persistence of immunity for the first 20 months following secondary immunization and compare it with the response and maintenance of antitoxic immunity following primary immunization. These observations are summarized for graphic presentation in chart 5.

It is apparent from table 19 that only 5.2 per cent did not show a response after the secondary immunization, as compared with 21.4 per cent failures in this group after the primary immunizations.[18] Also, there were almost twice as many

18. Four in this group were arbitrarily given low antitoxin values though the titrations done were not less than 0.03 units.

who had 1 unit or more of antitoxin after the secondary as compared with after the primary immunizations. Furthermore, there was for as long as 20 months relatively little tendency for the level of the lowest quartile to fall. This seems to indicate that the fortuitous stimuli encountered by this group made them better able to maintain a fair level of immunity (0.03 to 0.1 unit) after the secondary immunization, while after the primary immunization there was a tendency for some infants and children to lose their immunity six months after the completion of the injections.

COMMENT

This study, the primary object of which was to observe the responses of young infants to modern diphtheria toxoid and methods of administration, has succeeded in demonstrating that very young infants can be immunized against diphtheria.

In 83 per cent of the infants of the youngest age group, those infants less than 3 months of age at the initiation of their injections, protective levels of antitoxin developed after the primary vaccination. The appearance of protective levels in the youngest age group was occasionally delayed as long as six months after the the primary vaccination. The infants in the older age groups responded more promptly.

While it is not possible here to make exact comparison between the minimal responses of the younger infants and those of infants in the older age groups, it appears that the responses observed in the youngest group are not materially worse than those observed in infants 6 to 12 months of age, the age when diphtheria immunization is traditionally carried out, so far as the attainment of minimal levels of protection are concerned. It is, however, also apparent that those in the youngest age group did not obtain high levels of protective antitoxin as commonly as did those in the older age groups; only 7 per cent of the youngest infants achieved a level of 1 unit or more, as compared with 33 per cent showing such a level in the group of more than 12 months of age.

The presence of passive immunity also modifies the response to primary vaccination. When the degree of passive immunity is minimal, the response modification is also minimal, but when the degree of passive immunity is high the primary response is very poor. In those infants with passive immunity not only was the primary response poor but, even more striking, there was failure to maintain the immunity throughout the postimmunization period. In those infants with high degrees of passive immunity there was an inhibition of the capacity to respond to secondary immunization, as well as a failure in the primary response.

In comparing the effects of age and passive immunity, it appears that passive immunity has a greater disturbing effect on the production of primary immunity than does the age of the patient. Also apparent from these studies is the fact that the immunization course used in the study for diphtheria failed to provide an entirely adequate immunization even for the older age groups. Nine per cent of the infants 6 to 11 months of age and 14 per cent of the infants older than 12 months of age at the initiation of immunization failed to show responses higher than 0.03 of a unit. By the end of a year the antitoxin titers of 25 per cent of the infants and children in these age groups had fallen to this level or lower. It is unfortunate that the study did not enable us to see precisely how many would have fallen below the protective level of 0.003 unit at the end of the 13 month period.

It is also apparent from this study that even though the infants may not have had high levels of protective immunity after primary vaccination, in all except the small group who had high degrees of passive immunity at the time of their injections we were able to induce a capacity to respond to secondary vaccination, and the response to secondary vaccination was superior in all respects to the response to primary vaccination. Not only were higher levels of antibody obtained after secondary vaccination, but the antibody levels persisted at a higher phase throughout the ensuing 20 months, showing less tendency to fall off than they did during the 13 months following the primary vaccination.

When truly satisfactory basic immunity has been established, the children in this community have received at least enough fortuitous diphtheritic antigenic stimuli to maintain satisfactory levels of antitoxin. This situation may not hold true when more of the general population are artificially immunized.

These studies do not indicate the time and need for tertiary and later immunizations. It will require observations over very long periods to evaluate adequately these needs. We can, however, state that secondary immunizations a year after the initiation of the primary immunization are very highly desirable; necessary if one is to maintain an adequate level of immunity for a long period.

Studies in recent years [19] have shown that considerable degrees of purification of toxoids can be obtained without appreciable loss of the antigenic capacity of the toxoids. These efforts have not, however, been attended by the possible concomitant increase in the antigenic capacity of the toxoid preparations available. This has no doubt been in part due to the desire of the manufacturer to produce toxoids having very low reaction capacity. Such reactions are, of course, much more serious and important in adults than in infants, as it is largely in older children and adults that one finds those highly sensitive to the bacterial proteins, the most important cause of the reactions. It seems to us that it should be possible to increase the antigenic content of diphtheria toxoids used primarily in the immunization of young infants now. Barr and Glenny [4] have previously pointed out that we are probably using an amount of antigen inadequate to produce a satisfactory basic immunity, and our studies may be interpreted as further indication that an improvement in the antigenic capacity of toxoids is desirable.

The benefits to be derived from the increase of the antigens are, first, the establishment of sounder basic immunity and, second, a cutting down of the need for repetition of the booster immunizations.

It should be pointed out that the results reported do not represent the average results which one might expect to attain with the use of preparations generally available on the market at this time. Many of our preparations marketed do not contain the amount of antigen present in the toxoid preparation used in this study, and one may expect that many persons are now being vaccinated with antigens which yield very inferior immunity.

19. (*a*) Ross, V.: Preparation and Immunizing Properties of Protamine Diphtheria Toxoid, Am. J. Dis. Child. **68**:172-181 (Sept.) 1944. (*b*) Parfentjev, I. A., and Goodline, M. A.: Diphtherial Toxoid Purified by Absorption, J. Bact. **50**:661-666 (Dec.) 1945. (*c*) Holt, L. B.: Purified Precipitated Diphtheria Toxoid of Constant Composition, Lancet **1**:282-285 (March 8) 1947. (*d*) Pillemer, L; Wittler, R. G.; Clapp, F. L., and Adams, J. N., Jr.: Immunochemistry of Toxins and Toxoids: Preparation of Purified Diphtheria Toxoid for Clinical Use, J. Immunol. **58**:223-228 (March) 1948.

These studies bring sharply into focus the question of the feasibility of immunizing young infants against diphtheria and the question of combining diphtheria, tetanus and pertussis immunizations at the age necessary for the development of a satisfactory program for control of pertussis. It seems clearly established by this and other studies [20] that young infants can be immunized against diphtheria. Their relatively poor responses represent a quantitative rather than a qualitative difference in response capacity. This constitutes a challenge for the improvement of the immunization procedure.

Even with the present toxoids containing 30 to 40 Lf units a single immunization dose, it is entirely practicable to carry out diphtheria immunizations as early as at 6 weeks of life. When they are carried out at this early age it will be essential to use booster immunizations at a period 13 to 15 months after the primary immunization. This is, however, also true of immunizations in older age groups.

SUMMARY

The antitoxic diphtheria immunity of 573 young infants and children following combined immunization against diphtheria, tetanus, pertussis, typhoid and smallpox is presented with consideration of age and degree of passive immunity.

Two injections at an interval of three months of Lf units ± of aluminum hydroxide–adsorbed diphtheria toxoid induced relatively satisfactory levels of antitoxic immunity in 48 to 90 per cent of the infants and children tested in 69 per cent of the group as a whole. By the end of a year 23 per cent of the group as a whole and 30.6 per cent of those under 3 months when the injections were initiated had 0.003 unit of antitoxin and presumably would not be protected against diphtheria.

Young infants responded with lower titers of antibody than did older children and passive immunity inhibited the antitoxin response, particularly if the passive immunity was strong.

The effect of passive immunity in inhibiting response is compared with the effect of age. Passive immunity appears to be more significant than age in modifying the response.

The need for improvement of the diphtheria immunization antigens is pointed out.

The thesis that the capacity to respond to antigenic stimuli is a distinct phase of physiological maturation is not supported by these studies. The capacity of even very young infants to respond to diphtheria toxoid is such that they may be successfully immunized and their immunity will be adequate if the primary vaccination is followed by a recall injection after 10 to 15 months.

The maintenance of immunity following the recall injection is such in this community that one cannot predict the need for subsequent recall injections without further extended observations.

20. di Sant'Agnese, P. A.: Combined Immunization Against Diphtheria, Tetanus and Pertussis in Newborn Infants: III. Relationship of Age to Antibody Formation, Pediatrics **3**:333-343 (March) 1949. Vahlquist and others.[14] Parfentjev and Goodline.[19b]

IMMUNIZATION IN THE YOUNG INFANT

Response to Combined Vaccines: VI-X

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VI. TETANUS

IN THE preceding sections of these reports we have discussed methods, reactions and the specific antibody responses to pertussis and diphtheria antigens. In this section we shall consider the problems relevant to tetanus immunization.

In tetanus immunization of the young infant, and of older children and adults as well, one is dealing with a situation much less complex than those encountered in diphtheria and pertussis prophylaxis. There is for practical purposes no problem of preimmunization passive immunity to modify the response. Only one person in our group showed tetanus antitoxin before immunization. The exception was an older child who had been given passive prophylaxis. Furthermore, the antigen currently used is so devoid of reaction capacity that massive stimuli may be utilized in routine practice without fear of exciting significant reactions. This antigen uniformly evokes high levels of antitoxin and a high anamnestic capacity.

The effectiveness of tetanus immunization is attested by the Army experience in World War II,[1] when practically no tetanus occurred among personnel with adequate primary immunization and who received emergency stimulating injections at the time of being wounded. Actually there were only four such cases among 2,734,819 patients admitted for wounds, a rate of 0.11 per 100,000, as contrasted with a rate of 13.4 per 100,000 observed among United States Army personnel in World War I, when passive immunization with antitoxin at the time of injury was the only method of biologic prophylaxis. No doubt some of this improvement was due to the concomitant general reduction in infection resulting from the use of penicillin and sulfonamides, but in the main it is attributable to active prophylaxis with tetanus toxoid.

Even more significant was the fact that tetanus was not observed as resulting from insignificant lacerations and punctures which did not result in the administration of an emergency stimulating injection. Civilian practice experiences at Vanderbilt University Hospital [2] indicate that more than half of the cases of tetanus occur among people with trivial traumatic lesions, not of sufficient magnitude to require medical care.

From the Department of Pediatrics, Vanderbilt University School of Medicine.

1. Long, A. P., and Sartwell, P. E.: Tetanus in the United States Army in World War II, Bull. U. S. Army M. Dept. **7**:371 (April) 1947.

2. Peterson, J. C., and Christie, A.: Unpublished data.

While the question of general active immunization against tetanus might be a debatable proposition, the above observation reveals the fallibilities of relying on passive immunization as a means of eliminating tetanus in civilian practice. This and the ease with which tetanus immunization can be carried out concurrently with diphtheria immunization seem to be complete justification for the inclusion of the antigen in all preparations for routine diphtheria prophylaxis. It is also of significance that 70 per cent of the cases of tetanus [3] occur among persons of pediatric age.

In a preceding section of these studies we discussed the methods and materials used in these experiments, together with the resultant reactions.[4] Here it will suffice to repeat that the tetanus toxoid used was adsorbed on aluminum hydroxide, that two injections were given at an interval of three months and that each injection of toxoid was the toxoid equivalent of 100,000 MLD (minimum lethal doses) of toxin.

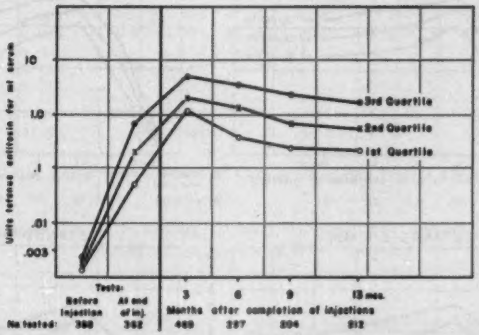

Chart 1.—Tetanus antitoxin levels following primary immunization among 573 infants and young children, by quartiles. The positions of the uncharted points are indeterminate because some serums were not titrated for < 0.03 unit.

TABLE 1.—*Tetanus Antitoxin Levels Following Primary Immunization Among 573 Infants and Children*

Antitoxin Titers	Test: Before Injection		Test: At End of Injection		Months After Primary Immunization: 3		6		9		13*		13¼		17		21		27		33	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
1.0	..	....	61	16.9	373	80.4	170	57.2	83	40.7	67	31.6	22	95.7	90	76.9	16	64.0	20	76.9	15	60.0
0.1	1	0.3	178	49.2	72	15.5	120	40.4	112	54.9	140	66.0	1	4.3	25	21.4	9	36.0	6	23.1	10	40.0
0.01	..	....	99	27.3	15	3.2	5	1.7	7	3.4	5	2.4	..	....	2	1.7	..	....	..	....	..	....
0.003	..	....	19	5.2	4	0.9	2	0.7	2	1.0	..	....	..	....	..	....	..	....	..	....	..	....
< 0.003	387	99.7	5	1.4	..	....	..	....	..	....	..	....	..	....	..	....	..	....	..	....	..	....
Total	388	100.0	362	100.0	464	100.0	297	100.0	204	100.0	212	100.0	23	100.0	117	100.0	25	100.0	26	100.0	25	100.0
Total < 0.1	387	100.0	123	33.9	19	4.1	7	2.4	9	4.4	5	2.4	0	....	2	1.7	0	....	0	....	0	....

* At the end of 13 months a secondary injection, 50 Lf units of tetanus toxoid, was given.

3. Noel, O. F., and McSwain, B.: Tetanus: A Study of 105 Cases, South. M. J. **43**:53 (Jan.) 1950.

4. Peterson, J. C., and Christie, A.: Immunization in the Young Infant: Response to Combined Vaccines, I.-IV., A. M. A. Am. J. Dis. Child. **81**:483 (April) 1951.

No definitive trials have been set up which would indicate the protective level for tetanus antitoxin immunity, though some authorities [5] have arbitrarily accepted 0.1 unit as being conservatively satisfactory and Descombey found that 0.1 unit would protect horses against tetanus infection and against large doses of toxin. It is quite probable that levels of 0.001 to 0.003 unit when associated with a good anamnestic capacity would be effective in preventing most if not all cases of naturally occurring tetanus.

Immediate Responses.—In table 1 and chart 1 are shown the antitoxin levels observed among the group as a whole, 573 children, following the primary vaccination. In this group 80 per cent had 1 unit or more of antitoxin per milliliter of serum three months after the primary vaccination, 96 per cent showed a level of 0.1 unit or

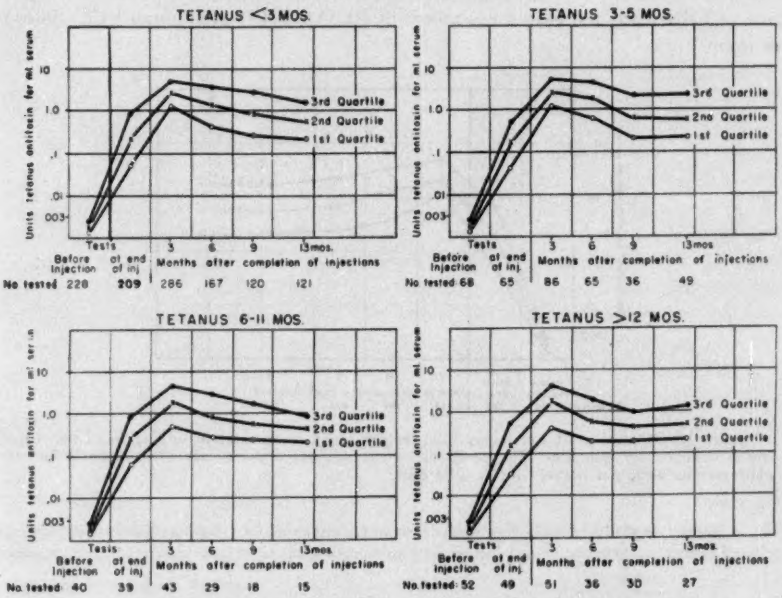

Chart 2.—Tetanus antitoxin levels following primary immunization among the various age groups, by quartiles. The positions of the uncharted points are indeterminate because some serums were not titrated for < 0.03 unit.

more and none had less than 0.003 unit. At six months after the primary vaccination many of the high titers had diminished but 98 per cent of the patients showed 0.1 unit or more. In the succeeding seven months this trend continued, but again 98 per cent of the group continued to show titers of 0.1 unit or more. During the 13 months after primary vaccination only eight out of 965 titrations revealed levels of less than 0.01 unit and none showed levels less than 0.003 unit.

These observations indicate that the primary antitoxin responses following the immunization course used are excellent, and one would anticipate that the entire

5. Edsal, G.: Medical Progress: Active Immunization, New England J. Med. **241**:18 (July 7); 60 (July 14); 99 (July 21) 1949.

group would be well protected against tetanus infection. Furthermore, there was a satisfactory maintenance of the antitoxic immunity for a year following the primary course.

Also shown in table 1 are the responses observed after the first stimulating, or booster, immunization, toxoid equivalent to 50,000 MLD of toxin, given 13 months after the completion of the primary immunization.

These observations indicate that immediate responses and the maintenance of antibody are at levels superior to those shown after the primary immunization. The

TABLE 2.—*Tetanus Antitoxin Levels Following Primary Immunization Among 352 Infants Aged Less than 3 Months When Injections Were Initiated*

Antitoxin Titers	Test: Before Injection		Test: At End of Injection		Months After Primary Immunization: 3		6		9		13*		13¼		17		21		27		33	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
1.0 or >.....	..	....	42	20.1	240	84.5	100	59.9	56	46.7	38	31.4	9	90.0	55	74.3	12	63.2	9	75.0	9	69.2
0.1.....	..	....	99	47.4	37	13.0	65	38.9	58	48.3	79	65.3	1	10.0	17	23.0	7	36.8	3	25.0	4	30.8
0.01.....	..	....	54	25.8	5	1.8	1	0.6	5	4.2	4	3.3	..	....	2	2.7	..	....	..	....	..	....
0.003.....	..	....	11	5.3	2	0.7	1	0.6	1	0.8	..	....	..	....	..	....	..	....	..	....	..	....
< 0.003.....	228	100.0	3	1.4	..	....	..	....	..	....	..	....	..	....	..	....	..	....	..	....	..	....
Total.....	228	100.0	209	100.0	284	100.0	167	100.0	120	100.0	121	100.0	10	100.0	74	100.0	19	100.0	12	100.0	13	100.0
Total < 0.1..	228	100.0	68	32.5	7	2.5	2	1.2	6	5.0	4	3.3	0	....	2	2.7	0	....	0	....	0	....

* At the end of 13 months a secondary injection, 50 Lf units of tetanus toxoid, was given.

TABLE 3.—*Tetanus Antitoxin Levels Following Primary Immunization Among 102 Infants Aged 3 to 5 Months When Injections Were Initiated*

Antitoxin Titers	Test: Before Injection		Test: At End of Injection		Months After Primary Immunization: 3		6		9		13*		13¼		17		21		27		33	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
1.0 or >.....	..	....	6	9.2	72	83.7	45	69.2	14	38.9	18	36.7	9	100.0	21	87.5	3	60.0	5	100.0	3	42.8
0.1.....	..	....	36	55.4	10	11.6	19	29.2	20	55.6	30	61.2	..	....	3	12.5	2	40.0	..	....	4	57.1
0.01.....	..	....	20	30.8	3	3.5	1	1.5	1	2.8	1	2.0	..	....	..	....	..	....	..	....	..	....
0.003.....	..	....	3	4.6	1	1.2	..	....	1	2.8	..	....	..	....	..	....	..	....	..	....	..	....
< 0.003.....	68	100.0	..	....	..	....	..	....	..	....	..	....	..	....	..	....	..	....	..	....	..	....
Total.....	68	100.0	65	100.0	86	100.0	65	99.9	36	100.1	49	99.9	9	100.0	24	100.0	5	100.0	5	100.0	7	99.9
Total < 0.1..	68	100.0	23	35.4	4	4.7	1	1.5	2	5.6	1	2.0	0	....	0	....	0	....	0	....	0	....

* At the end of 13 months a secondary injection, 50 Lf units of tetanus toxoid, was given.

primary immunization was, therefore, successful in establishing a satisfactory reaction or anamnestic capacity as well as in evoking a good antitoxin response.

The Effect of Age on Response.—In tables 2, 3, 4 and 5 and on chart 2 are shown the responses according to age groups. The differences in responses among the various age groups show no consistent or appreciable variation. Only five of 284, or 2.5 per cent, of the children in the age group less than 3 months, showed levels of less than 0.1 unit, while in the 6 to 11 month and the 12 month or more groups there were 9.3 and 7.9 per cent respectively who showed titers of 0.1 and 0.003 unit. Also a greater proportion of the youngest age groups attained the highest titers.

These studies indicate that with tetanus toxoid the antibody production in young infants is equal to or superior to that observed in the older infants and children, possibly indicating that with this antigen there was a great enough stimulus to evoke a maximum response and that the younger and smaller infants had better saturation of their tissues with the antigen.

The responses following the first booster injection, also shown in tables 2, 3, 4 and 5, are too few in number for a satisfactory comparison of the various age

TABLE 4.—*Tetanus Antitoxin Levels Following Primary Immunization Among 53 Infants Aged 6 to 11 Months at the Time Injections Were Initiated*

Antitoxin Titers	Test: Before Injection	Test: At End of Injection	Months After Primary Immunization: 3	6	9	13*	13¼	17	21	27	33
	No. %	No. %	No. %	No. %	No. %	No. %	No. %	No. %	No. %	No. %	No. %
1.0 or >.....	.. ....	8 20.5	29 67.4	13 44.8	6 33.3	3 20.0	1 100.0	9 100.0	1 100.0	4 100.0	1 33.3
0.1.....	.. ....	19 48.7	10 23.3	15 51.7	12 66.7	12 80.0	.. ....	.. ....	.. ....	.. ....	2 66.6
0.01.....	.. ....	10 25.6	4 9.3	.. ....	.. ....	.. ....	.. ....	.. ....	.. ....	.. ....	.. ....
0.003.....	.. ....	2 5.1	.. ....	1 3.4	.. ....	.. ....	.. ....	.. ....	.. ....	.. ....	.. ....
< 0.003.....	40 100.0	.. ....	.. ....	.. ....	.. ....	.. ....	.. ....	.. ....	.. ....	.. ....	.. ....
Total.....	40 100.0	39 99.9*	43 100.0	29 99.9	18 100.0	15 100.0	1 100.0	9 100.0	1 100.0	4 100.0	3 99.9
Total < 0.1..	40 100.0	12 30.7	4 9.3	1 3.4	0	0	0	0	0	0	0 ....

* At the end of 13 months a secondary injection, 50 Lf units of tetanus toxoid, was given.

TABLE 5.—*Tetanus Antitoxin Levels Following Primary Immunization Among Sixty-six Young Children Older than 12 Months When Injections Were Initiated*

Antitoxin Titers	Test: Before Injection	Test: At End of Injection	Months After Primary Immunization: 3	6	9	13*	13¼	17	27	33
	No. %	No. %	No. %	No. %	No. %	No. %	No. %	No. %	No. %	No. %
1.0 or >.....	.. ....	5 10.2	33 64.7	13 36.1	7 23.3	8 29.6	3 100.0	6 60.0	2 40.0	2 100.0
0.1.....	1 1.9	24 49.0	14 27.5	20 55.6	22 73.3	19 70.4	.. ....	4 40.0	3 60.0	.. ....
0.01.....	.. ....	15 30.6	3 5.9	3 8.3	1 3.3	.. ....	.. ....	.. ....	.. ....	.. ....
0.003.....	.. ....	3 6.1	1 2.0	.. ....	.. ....	.. ....	.. ....	.. ....	.. ....	.. ....
< 0.003.....	51 98.1	2 4.1	.. ....	.. ....	.. ....	.. ....	.. ....	.. ....	.. ....	.. ....
Total.....	52 100.0	49 100.0	51 100.1	36 100.0	30 99.9	27 100.0	3 100.0	10 100.0	5 100.0	2 100.0
Total < 0.1...	51 98.1	20 40.8	4 7.9	3 8.3	1 3.3	0	0	0	0	0 ....

* At the end of 13 months a secondary injection, 50 Lf units of tetanus toxoid, was given.

groups in this particular. They do indicate generally that there is in all age groups a satisfactory ability to respond to the stimulative injection.

Antibody Maintenance After Booster Immunization.—In table 6 and chart 3 are shown the levels observed among 148 infants and young children selected because they all had tests after the secondary immunization. From this table one can see that at 8, 14 and 20 months following the booster immunization high levels of antibody, 0.1 unit or more, were observed in all who were tested. This level of antibody is adequate protection against any conceivable infection.

The need for and the optimum time for further stimulating injections of toxoid are not indicated from these data.

Comment.—These studies indicate that an antigen stimulus equivalent to 200,000 MLD of tetanus [6] toxin in the form of an aluminum hydroxide–adsorbed toxoid is capable of evoking a high level of antibody in all infants and children, that the levels are adequate for complete protection and that a secondary stimulus will again raise and maintain for a long period a high level of tetanus antitoxin.

There is a need for further detailed study to determine whether or not and when additional stimulating injections need be given. It is conceivable that the establishment of a satisfactory basic immunity followed by one stimulating injection would be adequate to maintain protective levels of antibody for a considerably longer period than the 20 months of observation in this study. It is also conceivable that this degree of basic immunity would be satisfactory for protection for an indefinite time, that the possible infection subsequent to the immunization would

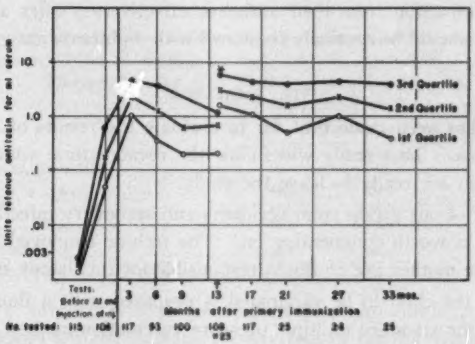

Chart 3.—Tetanus antitoxin levels following primary and secondary immunizations among 145 infants and children selected because they had been observed after the secondary immunization. The arrow indicates the secondary injection, 5 Lf doses of tetanus toxoid, and the asterisk, one week after the secondary injection. The positions of uncharted points are indeterminate because some serums were not titrated for < 0.03 unit.

TABLE 6.—*Tetanus Antitoxin Levels Following Primary Immunization and After the First Booster Immunization Among 148 Infants and Young Children*

Antitoxin Titers	Test: Before Injection No.	%	Test: At End of Injection No.	%	Months After Primary Immunization: 3 No.	%	6 No.	%	9 No.	%	13* No.	%	13¼ No.	%	17 No.	%	21 No.	%	27 No.	%	33 No.	%
1.0 or >.....	..	....	15	14.2	90	76.9	53	57.0	37	37.0	29	26.9	22	95.7	90	76.9	16	64.0	20	76.9	15	60.0
0.1.....	1	0.9	51	48.1	26	22.2	37	39.8	56	56.0	76	70.4	1	4.3	25	21.4	9	36.0	6	23.1	10	40.0
0.01.....	..	....	28	26.4	1	0.9	3	3.2	5	5.0	3	2.8	..	....	2	1.7	..	....	..	....	..	....
0.003.....	..	....	10	9.4	..	....	..	....	2	2.0	..	....	..	....	..	....	..	....	..	....	..	....
< 0.003.....	114	99.1	2	1.9	..	....	..	....	..	....	..	....	..	....	..	....	..	....	..	....	..	....
Total.....	115	100.0	106	100.0	117	100.0	93	100.0	100	100.0	108	100.1	23	100.0	117	100.0	25	100.0	26	100.0	25	100.0
Total < 0.1..	114	99.1	40	37.7	1	0.9	3	3.2	7	7.0	3	2.8	0	....	2	1.7	0	....	0	....	0	....

* At the end of 13 months a secondary injection, 50 Lf units of tetanus toxoid, was given.

6. While there is no exact equivalence between the number of MLD of toxin and Lf units of toxoid, this amount is probably not more than 100 Lf units of toxoid.

in itself serve to bring about an anamnestic response before the infection could produce a large enough amount of toxin to bring about its specific pharmacologic effect.

The observation that the youngest group of infants responds as well as or better than the older age groups to tetanus toxoid adequately repudiates the view as far as this antigen is concerned that there is a "physiological immaturity" of the immune response mechanism. It further suggests that the differences observed with respect to responses to diphtheria and pertussis immunizations are probably due to passive immunity, the lack of adequate stimulation and/or previous experience with the infection.

The general effectiveness of tetanus antigen, as reflected in these observations and past experiences, the freedom from associated reactions and the simplicity with which it can be combined with diphtheria and/or other antigens with addition to rather than detraction from their antigenic effectiveness offer adequate reasons why this antigen should be routinely combined with diphtheria antigen for immunizing children.

VII. SMALLPOX

No attempt has been made thus far to evaluate the results of immunizing our group to smallpox. That study will follow the revaccination which will be given when the children are ready to leave the study.

The freedom of our group from accidents and secondary infections from smallpox vaccination is worth commenting on. The technic employed and the instructions given to the mother are no doubt responsible for this happy situation.

The skin of the child to be vaccinated is prepared with a thorough scrubbing with ether, and the standard multiple pressure vaccination method with calf lymph vaccine is used. The excess vaccine is removed with a sterile dry sponge.

The mother is instructed to bathe the area daily with soap and water and to dry the area by blotting rather than rubbing. The usual loose clothes are allowed to cover the lesion, but no dressings, ointments or other applications are permitted; they are specifically proscribed. Significant secondary infections have not been encountered.

The primary vaccination from this small insertion is a small lesion which yields a discrete minimal scar.

VIII. TYPHOID

Typhoid vaccine was included in our vaccine complex because in this area typhoid immunization is desirable. The risks of typhoid are minimal until after the first year except in certain selected groups, and the only reasons for giving the vaccine at this time were for the purpose of simplifying the vaccination routine and to see if its inclusion would be tolerated.

Early in the study we made some attempt to evaluate the antibody responses by standard agglutination technics. The agglutinin levels were so erratic that we decided the study would be totally unsatisfactory. The inclusion of the typhoid vaccine has been continued with the expectation that the amount given would induce a primary immunity and that secondary injections would maintain reasonably satisfactory levels of protection.

We were not able to evaluate the amount of the reaction which could be attributed to the typhoid vaccine, and, while we are certain that it is appreciable, we have found from fairly extensive experience that infants have minimal reactions to typhoid vaccine and tolerate even larger doses well.

In most sections of the country there is no need for including typhoid vaccine as a routine vaccination procedure.

IX. THE INTERRELATION OF RESPONSES TO VARIOUS ANTIGENS

If the ability to form antibody is a question of physiological maturity then one would expect the ability to respond to one antigen would be approximately parallel to the capacity to respond to another antigen. In this study there are two antigens which have not evoked a maximum response, and it is of interest to correlate the ability to respond to one with the ability to respond to the other.

TABLE 7.—*Per Cent of Infants and Children Showing Low, Moderate and High Diphtheria Antitoxin Levels According to the Pertussis Agglutinin Titers Thirteen Months After Primary Immunization*

	Pertussis Agglutinin Titers		
Diphtheria Antitoxin, Units/Ml.	1/200 %	1/200 to 800 %	1/1600 or More %
0.01	44.4	54.5	45.8
0.01-0.1	44.4	40.0	45.8
1.0	11.1	5.5	8.4
Total	100.0	100.0	100.0

In table 7 we have correlated the responses to diphtheria antigen with the responses to pertussis antigen showing the per cent of infants and children at various levels of response.

According to this table there is apparently no increased ability to form diphtheria antitoxin resulting from a higher capacity to form Hemophilus pertussis agglutinins. This preliminary evaluation seems to be another step in the invalidation of the idea that ability to form antibody is primarily or even importantly a question of physiological maturation.

X. GENERAL IMMUNOLOGIC CONSIDERATIONS

The data presented above and in previous sections of the study [7] seem adequate to serve as a basis for discussing principles involved in immunization and in pointing out some of the deficiencies of current practices.

In the establishment of immunity by artificial devices, particularly by the injection of nonliving agents, either bacteria or their products, there are two fundamental aspects of the reaction which deserve careful consideration, namely the production of more or less circulating antibody and the establishment within the recipient of a capacity to respond in an anamnestic sense. Of these two aspects of immunity it is probable that the latter is more important and that the former cannot be obtained to any real degree without establishing some degree of the latter.

7. Footnote 4. Christie, A., and Peterson, J. C.: Immunization in the Young Infant: Response to Combined Vaccines: V., A. M. A. Am. J. Dis. Child. **81**:501 (April) 1951.

It is a well known immunologic principle[8] that it requires relatively large amounts of antigen to establish this capacity to respond, while minute amounts, even trace amounts,[9] may later serve as powerful stimuli to the established immunity.

The question of the desirability of trying to establish immunity against pertussis and possibly against diphtheria as early as practicable in life seems no longer to be a debatable question, though the method by which this can best be accomplished is still a moot question.

The possibility of protecting the young infant passively by the systematic immunization of women during pregnancy, while of considerable theoretical merit, has many disadvantages. These are the problems of administration and education which would be formidable. Also, our studies show that increasing the level and duration of the infant's passive immunity would serve to make more complex the problem of establishing an adequate primary active immunity. A new series of studies to determine the degree and duration of the induced passive immunity would be required before one could intelligently approach the question of immunizing the infant. We would, therefore, be inclined to dismiss the question of maternal immunization to protect the infant as an impracticable solution not suitable for general application.

As to the question of immunizing very young infants against diphtheria, it seems clearly established by this and other studies[10] that young infants can be immunized against diphtheria. Their relatively poor responses represent a quantitative rather than a qualitative difference in the response capacity and constitute a further challenge to improve the immunization procedure. Also it must be admitted that there is not a truly satisfactory antigen commercially available. As Barr and Glenny[11] have pointed out, we are probably using an amount of antigen inadequate to produce a good basic immunity. Studies in recent years have shown that considerable purification of toxoid without appreciable loss of antigenic capacity is quite feasible. These efforts have not resulted, however, in the marketing of a markedly more potent diphtheria toxoid. The primary reason for leaving the antigenic content of toxoids low is to avoid reactions. Sensitivity to bacterial proteins is much greater in the older age groups and is of far less significance in the immunization of younger age groups. Without further study, it would seem entirely practicable to increase the antigenic content of diphtheria toxoids, particularly those designed primarily for use in immunizing infants. This would establish a sounder basic immunity and reduce the need for frequent repetitive booster

8. Topley, W. W. C., and Wilson, G. S.: Topley and Wilson's Principles of Bacteriology and Immunity, ed. 3, Baltimore, William Wood & Company, 1946.

9. Glenny, A. T., and Allen, K.: The Schick Test Dose of Diphtheria Toxin as a Secondary Stimulus, J. Hyg. **21**:104 (June) 1922.

10. Jakóbkiewicz, J.: Immunization of Nurslings Against Diphtheria, Rev. d'immunol. **3**:70 (May) 1937. Vahlquist, B.; Murray, U., and Persson, N. G.: Studies on Diphtheria: Immunization Against Diphtheria in Newborn Babies and Infants, Acta Paediat. **35**:130, 1948. di Sant' Agnese, P. A.: Combined Immunization Against Diphtheria, Tetanus and Pertussis: III. Relationship of Age to Antibody Formation, Pediatrics **3**:333 (March) 1949.

11. Barr, M., and Glenny, A. T.: Some Practical Applications of Immunological Principles, J. Hyg. **44**:135 (April) 1945.

immunizations. Even with present antigens, however, with the equivalent of 30 to 40 Lf doses per milliliter or per single dose, it is practicable to carry out diphtheria immunization as early as at 6 weeks of life.

It is apparent that the immunity evoked by tetanus toxoid as reported in this study, and in most others currently, is very good. Not only is there a high level of antibody production, but also there is a tremendous capacity established to respond to minute stimuli. One comment worth making is that only very small amounts of toxoid are needed to bring about a good prompt anamnestic response; a tenth of the amount used in a single injection for basic immunization with present preparations should be ample and would be less likely to cause significant reactions, even in adults.

In pertussis immunization there is again a need for the establishment of a primary immunity characterized not only by the presence of a given level of antibody but also by a capacity to respond to stimulation by booster injections. The fact that 20 per cent or more of the infants and children given currently acceptable immunization courses fail to achieve protective antibody levels would seem to indicate that the antigenic values of the vaccines are too low. The study of Bell [12] showing "protection" among 71 per cent of the infants who received as few as 20,000,000,000 organisms is proof indeed that children may be protected and that some will be protected by relatively small antigenic stimuli but does not constitute any better proof of adequate basic immunization than does the reversal of the Schick test, and, furthermore, such results do not necessarily indicate the achievement of a satisfactory degree of immunization.

While we have been able to induce some immunity in all but 10 to 14 per cent of the infants and children and have produced relatively satisfactory immunity in 73 to 79 per cent by giving 80,000,000,000 aluminum hydroxide–adsorbed phase I H. pertussis organisms, it is our belief that this antigenic dose should be increased by 25 to 50 per cent in an effort to secure more consistently a more effective primary immunity. A larger antigenic dose would increase the number of infants and children showing some response and would induce protective levels in a still higher per cent of subjects.

While we are very anxious to see the appearance of vaccines which will produce little or no local or general reaction, we do not believe that moderate reactions should constitute a real bar to the use of an immunization procedure. Our experience has led us to believe that the proper education of the public as to the reactions to be expected and as to a method of reducing the severity of the reactions will remove the principal objections to reactions of the severity encountered. The measure for accomplishing the latter is relatively simple. For those infants who have relatively severe reactions the individual doses may be made fractional depending on the severity of the reactions and more injections to an equivalent total dose should be given.

The ideal time to initiate pertussis vaccination would seem to be at the time of the first or second visit to the well baby clinic depending on the infant's general health, usually, therefore, at 4 to 10 weeks of age.

12. Bell, J. A.: Pertussis Immunization: Use of 2 Doses of Alum-Precipitated Mixture of Diphtheria Toxoid and Pertussis Vaccine, J. A. M. A. **137**:1276 (Aug. 7) 1948.

While the above period may not be the ideal time to initiate diphtheria and tetanus and typhoid immunizations (in the communities in which this is desirable), we believe that the simplicity of giving these immunizations together and the fact that a given immunization program can be completed more regularly justify the use of triple vaccines. Furthermore, the early completion of the vaccination program would do much to lessen the incidence and degree of psychic trauma associated with the "shots."

The need for increasing the amount of antigen used for primary vaccination seems so apparent that we wish to propose the following schedule to serve until such time as more adequate vaccine preparations are available. The injections should, of course, be given only at such times as the child is in good health, free from intercurrent infections. The details of the schedule are shown in table 8.

This immunization course, while not ideal, could utilize presently available vaccines and should yield a general level of immunity high enough to provide general protection against the diseases involved and should improve our performance

TABLE 8.—*Injection and Dose of Vaccine for a Theoretically Desirable Prophylactic Immunization Program for Infants*

Injection No.	Age	Preparation	Amount
1	4-6 wk.	Pertussis vaccine	20-40 billion 0.5-1 cc.*
2	8-10 wk.	Pertussis vaccine	20-30 billion
		Diphtheria toxoid	30-40 Lf units
		Tetanus toxoid	25-50 Lf units
3	14-16 wk.†	Same as no. 2	
4	20-22 wk.	Same as no. 2	
5	76-80 wk.	½ dose given as no. 2	
6	60-70 mo.	½ dose given as no. 2	

* The number of pertussis organisms to be given with the first injection should be balanced to give 100,000,000,000 or more organisms for the total course.
† The intervals between the second, third and fourth injections may be permitted to vary widely and would be of little influence if they were from four to twelve weeks instead of the six weeks noted.

of routine immunizations. It further has the advantage of bringing out some of the quantitative aspects of immunization procedures now often poorly appreciated.

The use of the vaccines in combinations as outlined leads as a rule to the completion of primary immunization during the fifth month. This early completion of primary vaccination reduces tremendously the psychic trauma to the child incident to the "shots."

A booster injection composed of 10,000,000,000 to 20,000,000,000 phase I H. pertussis organisms, 4 to 10 Lf units of diphtheria toxoid and 5 Lf units of tetanus toxoid (with or without the addition of typhoid vaccine) should be given 12 to 16 months after the completion of the primary immunization or, as is usually more convenient, one half of the single injection doses of present day triple vaccines.

The need and time for subsequent secondary immunizations have not yet been elucidated either from the literature or from our own experience.

SUMMARY AND CONCLUSIONS

The immunologic responses of 573 young infants and children to combined immunization against diphtheria, pertussis, tetanus, typhoid and smallpox have been presented with reference to age at the time the immunization was initiated.

In tetanus immunization the effect of age on response is apparently of such minor consequence that it can be dismissed.

Tetanus toxoids equivalent to 50 Lf doses given in two equal injections at a three month interval evoke a satisfactory primary immunity.

A booster injection of toxoid given 13 months after primary vaccination yields a good immediate response and a level of protection sustained for more than 20 months.

The technic of immunization against smallpox in early infancy is mentioned.

The question of including typhoid vaccine with combined vaccines is briefly discussed.

An idealized combined immunization schedule for use in early infancy is proposed.

The administration of combined vaccines in early infancy is desirable because it greatly simplifies the establishment of a satisfactory immunization program. The psychic trauma from "shots" is diminished when the primary immunization is completed before the sixth month.

Complete combined booster immunizations should in all cases be administered 12 to 16 months after the primary immunization. A special combined vaccine for booster injections would be desirable.

The ability to respond with high levels of antibody to one antigen does not influence the capacity to respond to another antigen.

The authors were aided by many of the house officers of the Pediatric Service of the Vanderbilt University Hospital and by Mrs. Bernard Werthan, Mrs. Sam Small, Mrs. Harry Klein, Mrs. Harry Lipman, Mrs. Robert Eisenstein and Mrs. Edwin Raskin who volunteered secretarial aid and assisted in keeping the records. Dr. Margaret Martin performed the statistical analyses of the data and our secretary, Miss Anne Hudgens, assisted during the revisions of the tables and interpretations.

USE OF AN ANTIHISTAMINIC DRUG FOR TREATMENT OF THE COMMON COLD AT A SUMMER CAMP FOR BOYS

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WHETHER the antihistaminic drugs are of value in the prevention and treatment of the common cold in its early stages is still a controversial matter. Because of the widespread use of these drugs in the home and the possibly dangerous implications of their indiscriminate use, any further information on their efficacy is of value. An unusual opportunity presented itself for a controlled clinical study of antihistamine efficacy the results of which are described in this paper

In recent reports on the use of the antihistaminic drugs for the common cold different conclusions have been reached, and different methods of study have been undertaken. Several of these reports [1] concluded that the antihistaminic drugs did not seem to be more effective than the control medication. Of these three studies, one was performed on a small series in an army camp, the other two on large groups, the data being collected by mail and the patients taking medication at their discretion and noting the results. More recently, Baughn [2] presented a large study done over a 27 month period. Acetylsalicylic acid-acetophonetidin-caffeine combination (APC) was used as a control medication. His conclusion was that the antihistaminic drugs were significantly more effective than the control medication in the treatment of the common cold.

GENERAL PLAN OF STUDY

This study was conducted at a boys' summer camp in Maine. There were 260 boys between the ages of 9 and 16 and a staff of more than 100. The major portion of the data presented is from the studies of the campers. At the beginning of the season the campers were instructed by lecture that it would be most beneficial to them to be treated for their colds at the very earliest symptoms, for then the chance of cure was greatest and therefore there was less chance of their losing time from camp activities. Blanks were prepared, as shown in the accompanying form, to be filled in for each boy coming to the dispensary for treatment of a cold. Each boy who reported was examined, and his name was placed on a tally sheet if his symptoms had persisted for no more than 24 hours and it was believed that he was suffering from an uncomplicated common cold. A blank was completely filled out for him, and his name was entered in one of two columns to designate the therapeutic group in which he was enrolled. Patients were placed alternately in the two groups so that the selections were entirely at random. The only exceptions

1. Feller, A. E.; Badger, G. F.; Hodges, R. G.; Jordan, W. S.; Rammelkamp, C. H., and Dingle, J. H.: The Failure of Antihistaminic Drugs to Prevent or Cure the Common Cold and Undifferentiated Respiratory Diseases, New England J. Med. **242**:737 (May 11) 1950. Cowan, D. W., and Diehl, H. S.: Antihistaminic Agents and Ascorbic Acid in the Early Treatment of the Common Cold, J. A. M. A. **143**:421 (June 3) 1950. Hoagland, R. J.; Deitz, E. N.; Myers, P. W., and Cosand, H. C.: Antihistaminic Drugs for Colds, ibid. **143**:157 (May 13) 1950.

2. Baughn, W. L.: Antihistamine Chemicals in the Treatment of the Common Cold: Report on a 27 Month Study, Indust. Med. **19**:413 (Sept.) 1950.

to this grouping occurred with boys who were previously treated under this schedule and were returning for treatment of another cold developing at least 10 days after the previous one had ended. These boys were enrolled in the group they had not been placed in previously so that they could act as controls on themselves.

Every space must be filled in.
Date and time of onset of symptoms and signs are to be recorded.

P or T (encircle one)

Name..... Date..... Age..... Height..... Weight.....

Before		After	
Sniffles		**Sniffles**	
mild	severe	mild	severe
occasional	continuous	occasional	continuous
Sneezing		**Sneezing**	
mild	severe	mild	severe
occasional	continuous	occasional	continuous
Nasal Discharge		**Nasal Discharge**	
mild	severe	mild	severe
occasional	continuous	occasional	continuous
serous	purulent	serous	purulent
Nasal Obstruction		**Nasal Obstruction**	
mild	severe	mild	severe
occasional	continuous	occasional	continuous
Cough		**Cough**	
mild	severe	mild	severe
dry	wet	dry	wet
nonproductive	productive	nonproductive	productive
occasional	continuous	occasional	continuous
soft	harsh	soft	harsh
Throat		**Throat**	
scratchy	sore	scratchy	sore
Malaise	**Myalgia**	**Malaise**	**Myalgia**
Fever	**Ear Ache**	**Fever**	**Ear Ache**
Headache		**Headache**	

Before		After
Examination—Ear	**Temperature**	
Nose		
Throat		
Nodes		
General		

Remarks—
Final Diagnosis
Therapy—date started—
date ended —
dosage —
Results—
Reactions—
Treatment Schedule (check after each visit)

Breakfast—	**Lunch—**	**Supper—**	**Bedtime—**
Breakfast—	**Lunch—**	**Supper—**	**Bedtime—**
Breakfast—	**Lunch—**	**Supper—**	**Bedtime—**

Form filled out by physician

One group was given tripelennamine (pyribenzamine®) hydrochloride, 50 mg. four times daily for boys 12 years old and over and 25 mg. four times daily for boys under 12 years. The other group was given a white lactose tablet from a bottle labeled "T-22," a name picked by chance. These were given four times daily. Questions arising concerning the nature of the latter medication were answered by the statement that it was a new antihistaminic medicine as effective as tripelennamine in the treatment of colds. All therapy was continued for 48 hours despite cessation of symptoms. If at the end of this time symptoms still persisted, routine symptomatic therapy was started. No other medication was given during the 48 hours

of therapy under study. Each boy at the start of therapy was instructed that he must return four times each day, after meals and at bedtime, for treatment regardless of how he felt or the medication would not be effective. The only restriction of routine camp activity during therapy was of swimming. This was done merely to insure that all patients of both groups had similar activity schedules, for without such restriction some boys would be swimming and others would not. At the completion of therapy each boy was questioned specifically about the symptoms still present and the severity of these symptoms as compared with those at the start of therapy. In particular, an attempt was made to elicit a definite statement regarding the status of the cold. The matter of drug reaction was approached by the casual question: "Did you feel anything unusual during this treatment?"

TABLE 1.—*The Results of Early Treatment of Colds with Tripelennamine as Compared with a Control Medication*

	Tripelennamine	Placebo
Patients studied	37	37
Cured	11	11
Improved	17	17
No change	5	6
Worse	4	3
Side reactions	4	5

TABLE 2.—*The Results of Early Treatment of Colds of the Same Patient with Tripelennamine as Compared with a Placebo* *

Patient	Tripelennamine	Placebo	Side Reactions
D. A.	Improved	Cured	None
S. B.	Worse	Improved	Sleepy on tripelennamine
J. B.	No change	Worse	Sleepy on placebo
S. F.	Improved	Worse	None
W. F.	Cured	Improved	None
H. G.	Improved	Improved	Sleepy on tripelennamine
S. H.	Cured	No change	None
S. J.	Cured	Improved	None
I. L.	Improved	Cured	None
C. M.	No change	Worse	Sneezing on placebo
J. N.	Improved	Improved	None
R. W.	Improved	Cured	None

* Therapeutic courses were for separate colds occurring at least 10 days apart.

RESULTS

One hundred studies were done on 88 boys, 12 patients having two courses of treatment. For proper evaluation 26 records had to be discarded, 17 because of incomplete therapy and 9 because of complications occurring during therapy or shortly thereafter which made it evident that there was disease other than the common cold. Fortunately, the discard group was divided evenly between the test and control groups. There remained 37 cases studied in each group. For purposes of tabulation, each case was placed in one of four categories: cured, improved, no change and worse. Of the 37 patients treated with tripelennamine, 11 claimed cure, 17 improvement, 5 no change and 4 that they became worse during treatment. Of the 37 patients treated with a placebo, 11 claimed cure, 17 improvement, 6 no change and 3 that they were worse. The results in the two groups are almost identical.

Side reactions were surprisingly few. Four patients treated with tripelennamine complained of drowsiness, as did a similar number in the control group. In addition, one patient in the control group claimed that the medicine was causing him to "sneeze every minute."

Twelve patients received treatment with both drugs, hence, were their own controls. Of these 12 who received both forms of treatment, 5 reported better results with tripelennamine than with the placebo, 4 claimed better results with the placebo than with tripelennamine and 3 reported that the result was the same with both forms of therapy.

COMMENT

Since I was the physician in full time attendance at a large boys' summer camp in Maine during the summer of 1950, I was able to carry out this investigation with certain advantages not apparent in previous studies. In addition, the opportunity was present to study the effects of one of the antihistaminic drugs on a large group of adolescents. The following advantages were present throughout this study: All patients were under observation by a physician throughout the 24 hours of each day; the observation was not restricted to daily clinic sessions. More important than this, the general medical history as well as the personality disposition of almost all the boys was known intimately to the examiner through similar contacts in previous years. This fact in itself did not affect the selection of patients or evaluation of data to any significant extent, but it did enable exclusion from the study of patients who were of unstable or unreliable personality enough that reasonable evaluation of data might be invalidated. Similarly patients of known allergic nature were excluded. Exclusions were done so far as possible before the study was instituted. No one but I was aware of the true nature of the drug "T-22."

It is well known that the common cold may be difficult for the physician to diagnose and evaluate in the very early stages. Frequently an impending cold may be present without apparent physical signs. Most people evaluate their colds almost entirely by the symptomatology, at least in the very early stages, and are guided by these symptoms in deciding to use one of the popular antihistaminic medicines. With these facts in mind, it was felt that criteria such as the families use in the home would give the best basis for evaluation of these drugs for consumption in the home. With this method we would be better able to answer the question: "Does the taking of antihistaminic medication in the home prevent or cure the common cold in its early stages?"

SUMMARY AND CONCLUSIONS

In the clinical study presented tripelennamine proved no more effective than a placebo in the treatment and prevention of the common cold in its early stages.

There was no evidence from the study presented that tripelennamine caused side reactions in greater numbers or severity than did the placebo. Drowsiness was not a prominent reaction with a therapeutic regimen of tripelennamine.

It was evident in this study that the giving of medication for the common cold, be it placebo or tripelennamine, gave satisfaction to the majority of patients.

Guthrie Clinic.

STAPHYLOCOCCIC INFECTIONS IN HOSPITAL NURSERIES AND PEDIATRICS WARDS

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AN INCREASING number of reports have appeared in the current medical literature concerning the prevalence of infections in the newborn by penicillin-resistant strains of Staphylococcus aureus.[1] The purpose of this communication is to present certain clinical, epidemiological and bacteriologic observations on staphylococcic infections made in our nurseries during the period 1939 to 1950.

CLINICAL ASPECTS

Since 1939 our attention has been focused on recurring episodes of staphylococcic infection in the newborn at the Bronx Hospital. Most infections were of the skin or conjunctiva. In October and November 1941 there occurred a typical outbreak of epidemic diarrhea of the newborn, involving 19 babies.[2] Our studies seemed to indicate that a hemolytic, coagulase-positive Staph. aureus was the causative agent. Subsequent to this outbreak of diarrheal disease the hospital epidemiologist (W. W.) noted continuing sporadic cases of skin and conjunctival infection due to hemolytic coagulase-positive staphylococci during the period from 1941 to the present. In March 1950 our attention was directed to the following admissions to the hospital nurseries: three infants with empyema, two of whom had been born at the Bronx Hospital and one elsewhere; a fourth with

From the Departments of Laboratories and Research and Pediatrics, the Bronx Hospital, New York.

1. (*a*) Berger, K.: Über die Häufigkeitszunahme Penicillinresistenter pathogener Kokken, Wien. med. Wchnschr. **99**:536 (Nov. 19) 1949. (*b*) Finland, M.; Frank, P. F., and Wilcox, C.: In Vitro Susceptibility of Pathogenic Staphylococci to 7 Antibiotics, Am. J. Clin. Path. **20**:325 (April) 1950. (*c*) Plough, H. H.: Penicillin Resistance of Staphylococcus Aureus and Its Clinical Implications, ibid. **15**:446 (Oct.) 1945. (*d*) Eisman, P. C.; Marsh, W. S., and Mayer, R. L.: Differentiation of Antibiotics by Resistant Strains, Science **103**:673 (May 31) 1946. (*e*) North, E. A., and Christie, R.: Acquired Resistance of Staphylococci to Action of Penicillin, M. J. Australia **1**:176 (Feb. 9) 1946. (*f*) North, E. A.; Christie, R., and Rank, B. K.: Penicillin-Resistant Strains in Wounds, ibid. **2**:43 (July 13) 1946.

2. Felsen, J., and Wolarsky, W.: Epidemic Diarrhea of the Newborn, Arch. Pediat. **59**:495 (Aug.) 1942.

breast abscess, born elsewhere; a fifth with bacteremia, born elsewhere, and a sixth with abscess of the buttock, born at our hospital. All were infected with a hemolytic, coagulase-positive Staph. aureus. All strains were penicillin resistant but aureomycin sensitive.

All infants were apparently well at birth. The age at onset of clinical symptoms varied from 6 to 60 days. In nearly all instances signs of infection developed after the patient left the hospital. In case 5 there was definite hematogenous invasion, the same organism being recovered from the blood and the wound. In spite of an osteomyelitis of the entire shaft of the left tibia and a stormy clinical course, recovery was complete. An unusual feature of case 2 was defervescence to normal on the third day of illness, after penicillin therapy. A secondary rise in temperature occurred seven days later, with death in 16½ hours. The empyema had apparently been masked by antibiotic therapy.

The unique clinical feature in all cases was the unusual types of infection encountered (table), which had been practically nonexistent in our nurseries almost since the advent of antibiotics.

Six Cases of Unusual Staphylococcic Infection in the Newborn

Case	Clinic No.	Age, Days	Sex	Diagnosis	Born at *
1	223250	14	F	Empyema	B. H.
2	224247	30	F	Empyema	B. H.
3	224163	60	M	Empyema	O
4	224830	21	M	Breast abscess	O
5	220039	49	M	Staphylococcemia; osteomyelitis	O
6	224169	6	M	Abscess of buttock	B. H.

* B. H. indicates Bronx Hospital; O indicates other hospitals.

BACTERIOLOGIC AND EPIDEMIOLOGICAL ASPECTS

All of our strains were gram-positive cocci of small grain that produced a golden yellow pigment on solid medium, hemolyzed rabbit's blood, liquefied gelatin, produced acid from mannitol and were coagulase positive.

For a general review of the genus Staphylococcus, the article by Blair [3] should be consulted. In general, two characteristics of the organism appear usually to have parallel pathogenicity for man—the ability to cause hemolysis and the ability to clot plasma (coagulase positive). The fermentation of mannitol and the production of a typical yellow pigment also occur with considerable uniformity. Usually such strains are isolated from pus or blood. In addition to these characteristics, the cultural homogeneity and consistent penicillin resistance of our strains seemed to indicate a common pathogenicity and epidemiological background. Additional evidence of their homogeneity and of considerable practical importance in therapy was their universal sensitivity to aureomycin. Bacteriophage sensitivity tests [4] were carried out in cases 2, 3, 5 and 6 in an attempt to establish the common identity of the strains.[5] All proved to be type XIV. Identical findings were

3. Blair, J. E.: The Pathogenic Staphylococci, Bact. Rev. **3**:97 (June) 1939.

4. Fisk, R. T., and Mordvin, O. E.: Studies on Staphylococci: Further Observations on Bacteriophage Typing of Staphylococcus Aureus, Am. J. Hyg. **40**:232 (Nov.) 1944.

5. Dr. J. E. Blair and Miss M. Carr, Department of Bacteriology, Hospital for Joint Diseases, performed the bacteriophage typings and provided bacteriophage for our own subsequent typings.

obtained from studies of nine other babies with skin infections and from culture of swabbings from a bassinet and baby oil. With the realization that we were possibly dealing with epidemiologically related strains in all cases, an immediate survey of the nurseries and their occupants was undertaken.

The newborn service at the Bronx Hospital is comprised of three nurseries: one ward and two private. The nurseries are identified by the letters A, B and C, the first two being the private nurseries, while C is devoted to ward patients. A and B are located on the maternity floor of the hospital, adjacent to the labor and delivery rooms. C is located one floor above, adjacent to the children's wards and the ward maternity rooms. There is considerably more hospital traffic in the vicinity of the nurseries A and B than there is near nursery C. In each nursery 20 to 25 babies are accommodated.

Prior to July 1939 the nurseries of the hospital were comparatively free from contagion. In that month there began to appear infections of the skin in the form of impetigo neonatorum. At first the incidence was relatively low, six among 244 live births, but this slowly mounted over the following months so that in April 1940 the incidence was 40 among 220 live births. When the severity of the outbreak was realized, it was decided to assign one person to supervise the obviously necessary investigative and control measures. The hospital epidemiologist [6] was given full authority to establish isolation procedures, carry out bacteriologic studies and revise the apparently inadequate nursery routine. It was soon determined that the infecting organism was the hemolytic Staph. aureus, 15 consecutive cultures from the skin blebs revealing this organism in pure culture. Thereafter, sporadic cultures revealed the same organism. Coagulase tests were not done at that time.

Immediate control measures were established in the form of a modified unit system of nursery hygiene, a decrease in nurse-baby ratio and meticulous attention to minimizing the possibility of contact infections. As a result, the outbreak was sharply reduced by the following month. Thereafter, only sporadic cases of staphylococcic skin infections were noted. Nevertheless, the few cases that did occur made it appear that an endemic focus for staphylococcic infections had been established in the nurseries. From this endemic focus there occurred not only repeated minor outbreaks of skin infections but also eye infections in the form of staphylococcic skin infections were noted. Nevertheless, the few cases that did born [7] and the two cases of empyema and the one of abscess of the buttock in the newborn which are reported in this paper.

During World War II the nurseries were particularly overcrowded, and repeated sporadic outbreaks of staphylococcic infections were encountered. Accurate statistics could not be kept during this period because of the pressure of more urgent hospital problems, but it was apparent that the endemic focus was still present. From 1946 to 1950 more careful supervision was exercised in the nurseries, and only infrequent episodes were noted. These again were manifested as skin infections,

6. Felsen, J., and Wolarsky, W.: The Hospital Epidemiologist, Hospitals **14**:41 (Aug.) 1940.

7. Felsen, J.: Acute Focal Non-Specific Enterocolitis, Mississippi Valley M. J. **63**:20 (Jan.) 1941. Lyon, H. B. Jr., and Rantz, L. A.: Staphylococcus Aureus in an Outbreak of Infantile Diarrhea, Pediatrics **5**:617 (April) 1950. Felsen and Wolarsky.[2]

but in the form of a folliculitis rather than as impetigo neonatorum. Sample cultures done with material taken at varying intervals from the infected lesions on the skin were invariably positive for the Staphylococcus. A striking feature of these infections was their disappearance within 24 hours after 150,000 units of penicillin procaine had been injected intramuscularly. The sensitivity of the infecting organism during this period was in marked contrast to the penicillin-resistant strains described in the current report. Perhaps the massive dose given, considering the weight of the infected infants, was sufficient to overcome the relatively mild skin infections.

The current investigation was initiated in March 1950 when it was noted that between March 12 and March 26, 1950, three infants with staphylococcic empyema were admitted. From an epidemiological standpoint we were concerned only with the two indigenous cases. It was found that both babies were nursed in a temporary nursery established while nursery B was being painted. Both babies were cared for by personnel from nursery B. This nursery was apparently an endemic focus for the Staphylococcus, since for both babies and personnel cultures were positive for Staphylococcus when bacteriologic studies were made.

Thirty cultures were done with material taken from the nose, throat and rectum of babies in nurseries A, B and C. Twelve of these were positive (40 per cent) for hemolytic Staph. aureus; in nine the material was from the nose and throat, and in three, from the rectum. Material for cultures was taken from eight nurses in the same nurseries from the nose, throat or hands, and four (50 per cent) of the cultures were positive for the same organism. Environmental studies revealed air cultures to be positive for hemolytic Staphylococcus for nurseries A, B and C. Random cultures with material from various articles in the nurseries, such as lamp shades, baby cribs and diaper tables, were also positive for the same organism. Of 24 cultures from this entire group, 15 (63 per cent) were found to be type XIV by the bacteriophage method.[8]

Control cultures were taken in a similar manner in the pediatrics wards, in the bacteriologic laboratory and in adult medical wards. All of these were negative for hemolytic Staph. aureus. This confirmed our previous impression concerning the infectivity of the nurseries. One may assume, therefore, that for the three babies born at our hospital the etiological agent might have been acquired from the same source. Guthrie and Montgomery [9] have reported such an outbreak of staphylococcic pneumonia and empyema in 16 babies in one nursery. It is also of epidemiological significance to record that in a baby (case 6) born on March 23, 1950 and nursed in nursery B a staphylococcic abscess of the buttock developed which required incision and drainage before healing.

From the epidemiological point of view we have thus attempted to trace a series of staphylococcic infections occurring in our nurseries since 1939. The original outbreak was a major one of impetigo neonatorum; this was followed by a second major outbreak of epidemic diarrhea of the newborn; then there were sporadic skin and eye infections, and finally there was the unusual occurrence of two cases of empyema and one case of an abscess of the buttock.

8. Of 54 strains of hemolytic S. aureus recovered from various infections other than in the nurseries, only five (9 per cent) belonged to bacteriophage type XIV.

9. Guthrie, K. J., and Montgomery, G. L.: Staphylococcal Pneumonia in Children, Lancet **2**:752 (Nov.) 1947.

The occurrence of staphylococcic infections in nurseries is certainly not one limited to our own hospital or even to hospitals in our vicinity. Colbeck [10] reports two large outbreaks in Canadian hospitals. He emphasizes the importance of preventing air-borne infection of babies, since the initial stage of an epidemic is often respiratory in nature.

In connection with tests for penicillin sensitivity, it was interesting to find that 11 of the 12 strains tested in our cases were resistant to 8 to 64 units of penicillin per cubic centimeter. This corresponds to the observation of Herrell,[11] who reported that the number of strains of staphylococci which are resistant to penicillin has steadily increased during the past few years. Berger [1a] has also observed an increased frequency of penicillin-resistant strains of pathogenic cocci in the Staph. aureus group but not increased penicillin-resistance by gonococci, pneumococci or hemolytic streptococci. He states that "the increased frequency of penicillin-resistant Staphylococci is associated with the progressively increased therapeutic use of penicillin and with the fact that hospitals as centers of penicillin therapy become 'breeding places' of such strains." Finland and co-workers [1b] express a similar view, and Plough [1c] has noted the return of sensitivity to penicillin of previously resistant strains after a period without penicillin exposure.

At the Bronx Hospital it has been the practice for the past three years to administer 50,000 to 100,000 units of aquacillin® daily to all premature infants weighing less than 5 pounds (2,268 Gm.). It is possible that under this regimen penicillin-resistant staphylococci may have developed while the infants themselves remained well. Similarly, the widespread use of penicillin for impetigo and other skin infections in nurseries has led to the occurrence of occasional cases in which infants, at first apparently well, later relapsed, with the development of penicillin-resistant staphylococci.

From a therapeutic point of view it was of importance to determine whether resistance to aureomycin was also characteristic of the strains reported in our study. This was not so, since all the strains tested (22) were found to be sensitive to aureomycin. Herrell [11] has commented on the rarity of aureomycin-resistant strains of pathogenic cocci.

After an interval of two months bacteriologic studies of the nurseries were again performed. It was found that cultures positive for Staphylococcus were repeatedly obtained for nurseries A and B but not for nursery C. This corresponded with the clinical finding of repeated skin and eye infections at the usual level in nurseries A and B and almost none in nursery C.

PROPHYLAXIS

The cases reported above, together with other published reports, point to the need for more extensive attention to the problem of staphylococcic infections in the nurseries of hospitals. One often reads of the low incidence of a particular disease in the newborn because of their sheltered existence. Increased birth rates and the almost universal practice of hospital deliveries have placed a tremendous

10. Colbeck, J. C.: Extensive Outbreaks of Staphylococcal Infections in Maternity Units: The Use of Bacteriophage Typing in Investigation and Control, Canad. M. A. J. **61**:557 (Dec.) 1949.

11. Herrell, W. E.: Aureomycin, Am. J. M. Sc. **219**:570 (May) 1950.

burden on the already overtaxed physical capacities of the average nursery. The sheltered existence no longer exists. With overcrowding come opportunities for infections of all varieties—impetigo, empyema, diarrhea of the newborn, conjunctivitis and thrush. The first step in the prophylaxis of all of these infections is proper planning for the establishment of more and smaller nurseries. The recent plan of rooming in of babies with mothers in small units may be a solution. Montgomery and co-workers [12] report on 1,018 newborn babies cared for in this way at the Jefferson Medical College Hospital and report that "in the 1,018 full term babies housed with the mother, there have been no cases of diarrhea or impetigo and only one case of mild (questionable) respiratory infection." At present it appears most feasible to focus attention on conditions as they exist in most of our nurseries today. Meticulous nursery hygiene is essential. Frequent cleansing of the physical equipment of the nurseries with soap and water, supplemented with use of antiseptics and painting, may eradicate persistent foci of infection in cribs, tables, lamps and so on. A continued educational program among the nursing staff must be instituted, particularly where the turnover of nursing personnel is high. Careful cleansing of the hands after each baby is handled is imperative. The use of antiseptic solutions for the hands after the handling of babies is generally impractical. The use of soap and hot water and orange stick for the nails appears to be satisfactory. The use of detergents and one of the newer antiseptics, such as hexachlorophene, for scrubbing before going on duty may ultimately prove more effective. We are now using the septisol® (with hexachlorophene 0.75 per cent) technic. Nurses usually avoid the repeated use of all antiseptic solutions which are irritating or discoloring to the skin. Change of station or relief from duty for all nurses with upper respiratory tract, intestinal or skin infections will remove possible carriers from contact with susceptible infants. The problem of the face mask is one that has never been satisfactorily solved. In our nurseries masking is required of all occasional visitors to the nurseries, for example, physicians, residents and maintenance personnel, while nurses who constantly work in the nurseries, and who are presumably free of infection, are permitted to work unmasked.

Centralized responsibility is essential for adequate control. A notification system for suspected infectious disease is imperative in order to effect rapid diagnosis and isolation. The hospital epidemiologist fills this purpose admirably. He should be in close touch with the laboratory and clinical departments of the hospital. Such a physician may be chosen from among the younger members of the staff and receive a short course of training at one of the accredited schools of public health. The slight expense involved will be more than compensated for by the resulting comparative freedom from outbreaks and their attendant expense and unfavorable notoriety.

Finally, one must consider the use of either antibiotic or chemotherapeutic agents for prophylaxis. The use of aureomycin, 50 mg. in one bottle daily, is suggested for the average newborn infant during the period of hospitalization. We

12. Montgomery, T. L.; Steward, R. E., and Shenk, P. E.: Observations on the Rooming-In Program of Baby with Mother in Ward and Private Services, Am. J. Obst. & Gynec. **57**:176 (Jan.) 1949.

are now using the new crystalline aureomycin [13] in the dosage specified, and it appears to be relatively free of such effects as nausea and diarrhea up to the present writing. This antibiotic possesses a wide therapeutic spectrum and appears to be relatively free from the danger of development of aureomycin-resistant strains. Studies at present in progress on our newborn are aimed at determining the minimal blood level of aureomycin which will protect against the staphylococcic infections prevalent in our nurseries. Its effectiveness is being evaluated under adequate control conditions, and a final report will be submitted subsequently.

Chandler and co-workers [14] reported the successful use of aureomycin in curative therapy during a staphylococcic outbreak in a newborn nursery in Baltimore.

It is hoped that with the use of this antibiotic for prophylaxis a sufficiently high blood level will be obtained to counteract the minimal infections that are so frequently encountered in nurseries. As these are diminished one might expect the incidence of the more serious infections to fall. It is an epidemiological principle that epidemics do not occur until a sufficiently high carrier level is reached. If one can keep the carrier level below the critical point, then disastrous outbreaks will not occur.

SUMMARY

We have presented six unusual cases of penicillin-resistant staphylococcic infections in the newborn, three of them occurring within the same month in babies born at our hospital. From studies carried out since 1939 it appears that there has been a continuous chain of events due to the same organism, involving cases of impetigo neonatorum, epidemic diarrhea of the newborn and skin and eye infections and ending with the present reports of empyema, osteomyelitis and abscess of the buttock. Prophylactic and curative therapy with aureomycin is suggested, based on the demonstrated sensitivity of the staphylococci to this antibiotic.

13. The aureomycin was supplied for research purposes by Dr. Philip Boyer, Lederle Laboratories Division, American Cyanamid Company, Pearl River, N. Y.

14. Chandler, C. A.; Schoenbach, E. B., and Bryer, M. S.: Observations on Staphylococcal Infections Treated with Aureomycin, Pediatrics **4**:149 (Aug.) 1949.

SIMPLIFIED TRANSPARENT TUBERCULIN PATCH TEST

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THE TUBERCULIN patch test has been modified by the use of Scotch® cellophane tape instead of adhesive tape, by the use of only one, a smaller, tuberculin test square instead of two and by the omission of the control test square and the protective crinoline. This simplified test seems to offer several advantages which make it suitable for mass testing, while the original tuberculin patch test retains its place for individual testing.

MATERIAL

Commercially available Scotch® cellophane tape having a width of ¾ inch (1.9 cm.) is unrolled, and on its adhesive side thin tuberculin-containing filter paper patches are placed at 1 inch (2.5 cm.) distances (fig. 1). These filter paper pieces have a cross or square form

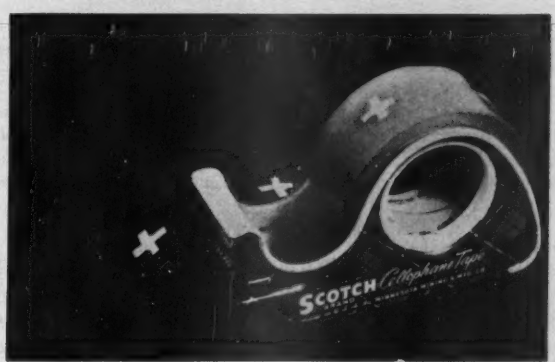

Fig. 1.—Transparent tuberculin patch tests ready for use.

and a surface of only 25 sq. mm., one fourth of the size used in the original tuberculin patch test. They are saturated with tuberculin produced on a synthetic medium and having four times the strength of standard tuberculin, as employed in the original tuberculin patch test (Lederle). No control squares are used. The tape is then rerolled, and the tests are ready for use. As can be seen in figure 1, Scotch® cellophane tape is available in rolls in a metal dispenser with a sharp edge on which the tape can easily be torn off. This permits cutting the tape in the middle between two tuberculin patches; thus, individual strips, ¾ by 1 inch, containing only one tuber-

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culin test square are delivered. The adhesive surface of these tests does not need to be covered with crinoline, since the next layer of tape on the roll offers a sufficient protection. The dry tuberculin-filter paper patches adhere firmly to the adhesive side of the tape and not to the smooth cellophane surface of the next layer on the roll.

METHODS

In order to compare the efficacy of this simplified test with that of the original tuberculin test, the same batch of tuberculin-containing dried filter paper was used in the preparation of both tests. All the tests were applied to symmetrical skin areas of the back or the volar surface of the forearms, because of the known variability of skin sensitivity in different sites of the body. The skin areas were cleaned with acetone when this was necessary. In the majority of cases such cleaning was omitted, with the exception of a few instances in which the skin was excessively oily and neither test would adhere properly without previous defatting of the skin.

The tests were applied and removed simultaneously and were kept in place for 48 hours. While the tests were in contact with the skin, bathing or wetting of the test area was avoided. The skin reactions were read at the time of removal and 24 and 48 hours after removal of the tests. For the transparent tests additional readings were done 24 and 48 hours after their application.

For a comparative evaluation, measurement of the skin reactions to the two tests was unsuitable. Since the original tuberculin patch test contains two tuberculin test squares, each

Comparative Results of Tests

Cases	Number	Tuberculin Patch Test		Transparent Patch Test	
		Positive	Negative	Positive	Negative
Children with active or healing tuberculosis	38	38	0	38	0
Children without evidence of tuberculosis	330	17	313	17	313
Nurses without evidence of tuberculosis	43	5	38	5	38
Total	411	60	351	60	351

having a four times larger surface than the single test square of the modified test, more extensive skin reactions to the former were to be expected. Therefore, only the intensity of the reactions could be compared. This was done by judging the degree of induration and the density and intensity of the lichenoid-follicular eruption rather than by metric determination.

COMPARATIVE EVALUATION

A total of 411 persons, 368 children and 43 student nurses, were tested. Among the children 38 were known to have active or healing tuberculosis. As shown in the table, 55 children and 5 nurses showed a positive reaction and 313 children and 38 nurses, a negative reaction to both tests. In not a single case was there disagreement between the reactions to the two tests. The intensity of the two reactions was slightly different in a number of cases but never to a degree that one reaction was doubtful while the other was unequivocal nor in a distribution which would indicate the superiority of one test to the other. For all practical purposes, the reactions to the two tests showed a complete conformity.

In all but three positive reactors the skin reaction was visible through the transparent tape 24 hours after the application of the test. It appeared as erythema and swelling around the edges of the filter paper patches (fig. 2) and was unequivocal in all cases; in most of the cases it became more intensive 48 hours after application, before the modified test was removed.

Unspecific skin reactions were more frequent with the use of adhesive tape than with the use of cellophane tape. Most of these adhesive reactions consisted of a transient erythema which had disappeared 24 hours after removal of the test. Such mild unspecific reactions were almost absent with the use of cellophane tape. In the whole group, three patients showed a severe unspecific reaction to adhesive and only one to cellophane tape; these severe unspecific reactions were still visible 48 hours after removal of the test, but did not interfere with the interpretation of the reaction to tuberculin. Fifty additional patients were tested with the cellophane tape alone (without tuberculin); none of them showed any skin reaction. The adhesive mass of cellophane tape consists of rubbers and resins which seem to have little antigenicity, though they are not completely free of it.

There was some disagreement between us about the adhesive quality of the two tests. One of us felt that the cellophane tape was of inferior adhesive quality. It is

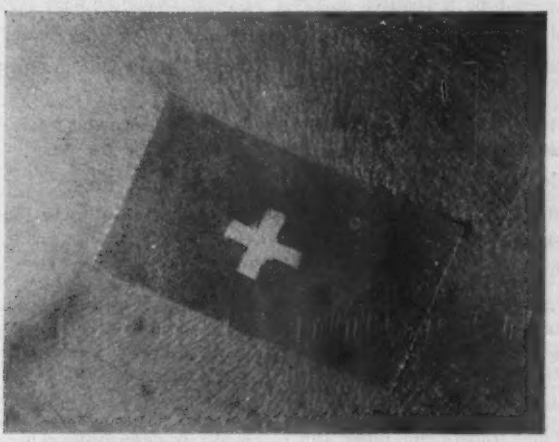

Fig. 2.—Transparent tuberculin patch test 24 hours after application, showing positive skin reaction.

true that the edges of this tape easily curl up, but none of the modified tests actually came off the skin. There was only one exception, in a patient having an excessively oily skin; both tests fell off this patient but stuck equally well after the skin was defatted with acetone. Perspiration during hot summer days did not cause either test to come off the skin. On the other hand, even short immersion of the modified test into water separated the cellophane from the adhesive mass, the latter remaining as a thin film attached to the skin. The adhesive tape of the original patch test is not similarly affected by water. Another difference between the two adhesive materials exists in that cellophane tape sticks immediately to the skin, while adhesive tape, kept in the refrigerator, adheres better after approaching skin temperature. This seems to be in favor of cellophane tape; however, cellophane tape is more vulnerable to excessive climatic factors. Under very dry conditions the cellophane backing becomes dry and brittle after a while; under very humid conditions the cellophane absorbs moisture, and the adhesive quality will be reduced after prolonged exposure. The general impression was that under normal

conditions both the original and the modified patch test show a satisfactory adhesive quality. Even a short immersion into water is prohibitive with the use of the modified test, while this is not true for the original patch test.

COMMENT

In our hands, the original tuberculin patch test and the simplified transparent test seemed to be equally reliable. As compared with the original test, the modified test showed the following advantages and disadvantages. The advantages are these:

1. It saves time by not requiring removal of crinoline and by sticking immediately to the skin.

2. It makes positive reactions visible at their onset and permits removal of the test prior to 48 hours; thus, unduly strong reactions are avoided.

3. It produces smaller skin reactions, thus decreasing all disagreeable local sensations caused by a positive reaction (for example, itching), as well as the risk of focal and general constitutional reactions.

4. It causes somewhat less unspecific irritations of the skin due to the adhesive material.

5. It causes less wrinkling owing to the smaller size of the test.

The disadvantages of the modified test are these:

1. It is less stable and more vulnerable to climatic conditions.

2. It comes off the skin when immersed into water even for a short time.

3. It lacks a control; since reactions to the control test square are very rare, this is a minor disadvantage.

4. Though not evident in this study, the smaller size of this test and the use of only one tuberculin test square instead of two may in rare instances cause a positive reactor with low sensitivity to tuberculin to be missed.

SUMMARY

A simplified transparent tuberculin patch test is described. This modification uses Scotch® cellophane tape instead of adhesive tape, only one, a smaller, tuberculin test square instead of two and omits the control test square as well as the protective crinoline.

A comparative evaluation on 368 children and 43 nurses showed a 100 per cent conformity between the reactions to the modified and the original tuberculin patch test. There were 60 positive and 351 negative reactors to both tests.

Through the transparent tuberculin patch test positive reactions are visible at their onset. This permits removal of the test prior to 48 hours and avoids unduly strong reactions. Several other advantages and disadvantages of the test are outlined.

This modified test may be useful for mass testing.

Case Reports

CONGENITAL WEB OF THE LARYNX

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BETWEEN 1932 and 1949, with approximately 4,000 patients admitted a year, only nine cases of laryngeal web have been diagnosed at Babies Hospital. This suggests that the lesion is relatively rare. In a review of these cases and those in the literature, it has been found that most webs are thin bands across the anterior margins of the vocal cords. Following is a report of a case of a markedly deforming web recently seen in Babies Hospital which is unlike any seen here previously or described in the literature.

REPORT OF A CASE

The patient was a 6½ month old Negro boy, who was admitted to Babies Hospital on April 27, 1949, at the age of 7 weeks, with a complaint of stridor, which became worse on inspiration, since birth. Both parents were alive and well. There were four siblings, aged 9, 8, 6 and 4 years, all alive and well. The mother had had one spontaneous miscarriage at three months. The present pregnancy had been complicated by nausea and vomiting in the first seven months. The infant was born by a normal full term spontaneous delivery. His birth weight was 7 pounds 6 ounces (3,350 Gm.), and he breathed immediately. In the neonatal period he was vigorous and showed no cyanosis or jaundice. Since birth he had inspiratory and expiratory stridor with retraction of the sternum and supraclavicular areas. He seemed to be more comfortable in a prone position. He had been unable to phonate until two weeks before admission. When admitted he had not quite regained his birth weight. His appetite, formerly poor, was good at this time. He could suck and swallow without difficulty but usually vomited projectilely after meals. He held his head up at the age of 3 weeks and lacrimated when he cried, although he made no sound.

Physical Examination.—At the time of admission, examination revealed a well developed and thin male infant weighing 3,240 Gm. and measuring 53 cm. in length who did not appear acutely ill. He had a high-pitched inspiratory crow with moderate retraction of the xiphoid area of the anterior wall of the chest. When he was stimulated, the cry was weak, high pitched and hoarse. There was no cyanosis. The lungs were clear on percussion. On auscultation there were noted questionably diminished breath sounds obscured by transmitted laryngeal sounds. Results of the remainder of the physical examination were within normal limits.

Laboratory Examination.—The initial blood cell count showed 4,080,000 red cells and 5,900 leukocytes per cubic millimeter, with 54 per cent polymorphonuclear leukocytes, 42 per cent lymphocytes, 3 per cent monocytes and 1 per cent eosinophils. The hemoglobin content was 10.5 Gm. per 100 cc. After the first week the leukocyte count ranged between 5,000 and 15,000 with a normal differential count. Occasional increases in the total white blood cell count were associated with mild respiratory infections. The hemoglobin gradually fell to 7 Gm. per 100 cc. and the red blood cells to 3,510,000 per cubic millimeter. He was given a transfusion of 80 cc. of whole blood, type O RH-positive, about three months after admission. The hematocrit reading three days later was 32. Examinations of the urine gave results that were all within normal limits. The reaction to the Mazzini test was negative.

Course in the Hospital.—On direct laryngoscopy, the day after admission, the examiner reported a congenital web of the larynx which "appeared to have its origin on the false cord area and extended from the anterior commissure almost to the end of the vocal process of the

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arytenoid cartilage. Only a small chink remained posteriorly." Three days after admission a tracheotomy was performed, after which there was a mild rise in temperature. Roentgen studies six days later showed consolidation of the upper lobe of the right lung, and procaine penicillin (crysticillin®) in doses of 300,000 units each day was administered and maintained for 30 days, although his temperature fell to normal two days after the tracheotomy. He was maintained on a tracheotomy regimen. He gained weight steadily, although he regurgitated or vomited a portion of every feeding. Throughout the remainder of his life he had several unexplained temperature elevations with response to procaine penicillin. A mild episode of diarrhea, during which enteric pathogens were not found on bacteriologic examination, was associated with one rise in temperature. On another occasion some fragments of glass were found in the tracheotomy tube, and there was a slight elevation in temperature two days later. Some blood-tinged mucus was obtained on suction for the following two weeks, and once during this period he became apneic and cyanotic. However, he responded to artificial respiration and an hour later, after being placed in an oxygen tent, appeared normal. This occurred about one month before death. Thereafter he did well until the night before death, when he was noted to be cyanotic and in a cold sweat. On the morning of death he vomited his early feeding. One and a half hours later he was found apneic and cyanotic, and no heart beat could be heard. Formula poured out of his mouth and nose. He did not respond to artificial respiration, intracardiac injection of epinephrine or oxygen via the tracheotomy tube and was pronounced dead.

Clinical Diagnosis.—The clinical diagnoses were congenital deformity (laryngeal web), operation (tracheotomy) and presumed aspiration of vomitus.

Postmortem Macroscopic Observations.—External examination revealed the body of a well developed and well nourished Negro boy weighing 6,710 Gm. and measuring 64 cm. in length. Apart from the tracheostomy, at the level of the first tracheal ring, no abnormalities were noted externally or in the body cavities.

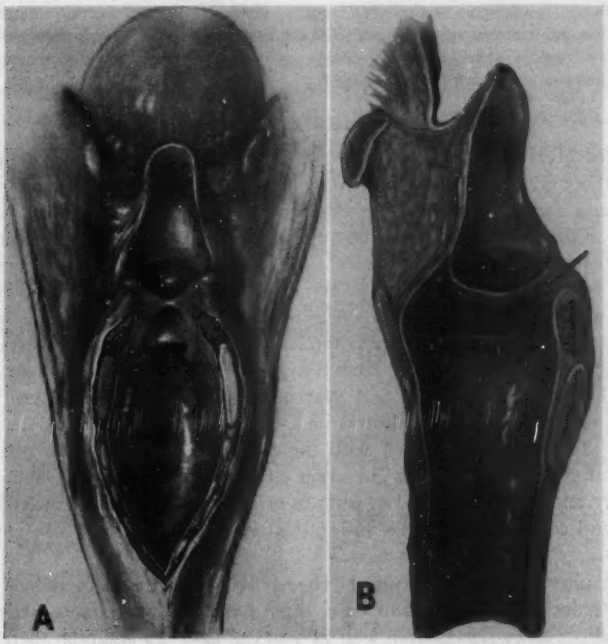
Larynx and Trachea.—The most significant findings were in the larynx and trachea. The epiglottis appeared somewhat small and deformed (fig.). The opening into the larynx presented two orifices. The posterior one was a small slitlike opening 2 to 3 mm. in anteroposterior diameter and 1 mm. in transverse diameter. The anterior opening was larger and measured 4 mm. in anteroposterior diameter and 6.5 mm. in transverse diameter. It opened into two blind pouches approximately 1 cm. deep. Between these, running in an anteroposterior direction, was a rounded elevation 2 mm. in height. The posterior orifice opened into a passage 4.5 mm. in length and 2 to 3 mm. in anteroposterior diameter. Below this the trachea quickly resumed its normal dimensions, so that the portion enclosed by the cricoid cartilage was approximately normal. The anterior wall of this narrow passage was formed by the posterior part of the abnormal web. The web itself was pink and firm. It was not over 1 mm. in thickness and appeared relatively avascular. The posterior portion was as thick as the remainder of the web. Its two halves were symmetrical. No scarred areas were noted. The membrane, or web, was attached to the lateral walls of the passage along the false vocal cords and anteriorly in a line extending evenly between these. Posteriorly it extended up the vocal processes and medial aspects of the arytenoid cartilages so that this part was almost at a 90 degree angle with the wide anterior portion of the web. Just below the line of attachment at the false vocal cords small ventricles were seen. These were shallower than usual. Beneath these, short translucent linear cords, about 4 mm. in length, representing the true vocal cords, ran in a normal direction. Their posterior ends were attached to the vocal processes of the arytenoid cartilages. At the level of the first and second tracheal cartilages a patent tracheostomy was present in the anterior wall. Just cephalad to this and occluding the lumen of the trachea was a pink nodule of granulation tissue, measuring 9 by 4 by 4 mm., which was adherent to the anterior and lateral walls of the trachea. On the posterior tracheal wall just opposite the tracheostomy was an ulcer 2.5 cm. long and 5 mm. wide which extended down the posterior tracheal wall and terminated 2 cm. above the carina. Its margins were thickened and elevated. The remaining wall of the trachea was congested. The trachea contained a yellowish pink foamy material. Numerous brick red paratracheal lymph nodes were evident.

Heart: The heart and great vessels weighed 50 Gm. The right ventricle and tricuspid valve were moderately dilated.

Lungs: The lungs were mottled pink and purple. The right lung weighed 74 Gm. and the left lung 76 Gm. The upper lobes were crepitant, and the lower lobes were firm. There was an accessory fissure in the lower lobe of the right lung. The cut surfaces were a beefy red, and on pressure a foamy pink material exuded from the lower lobes. The large bronchi were filled with a yellowish pink foamy material, and their walls were congested.

Gastrointestinal Tract: The gastrointestinal tract was congested throughout. Gross examination of the spleen, liver, pancreas, adrenal glands, kidneys, pelvic organs and thyroid gland revealed no abnormalities. The brain appeared normal except for congestion of the leptomeninges.

On postmortem bacteriologic examination of the blood a nonhemolytic Staphylococcus albus grew out which was mannitol and coagulase negative. Six days later one colony of the same organism grew out on a pour plate.



A, the larynx and trachea viewed from behind. The small posterior airway has been opened and is spread widely to show the web. The large blind anterior orifice is seen. The vocal cords lie just beneath the web. *B*, a sagittal section of the larynx and trachea. The saclike web lies just above the ventricle. The arrow indicates the posterior airway.

Microscopic Examination.—Heart: No abnormalities were seen.

Lungs: In most fields the alveoli were partially collapsed. Their walls were thickened with engorged capillaries and irregularly shaped small mononuclear cells. The alveoli contained variable amounts of red blood cells, pink granular material and large phagocytes. Some of these phagocytes were doubly nucleated and brown. In some fields the alveoli were completely filled with this material. The atria were frequently dilated. The bronchi contained small amounts of red blood cells, phagocytes, pink granular material and debris. One was packed with red blood cells, granular debris and desquamated epithelium.

Trachea: This section was taken through the ulcer and its marginal tissue. The epithelium near and at the margin was of stratified squamous type. The ulcer had a necrotic surface over a fibrous base. About some of the submucosal glands there was an infiltration of plasma cells. The

capillaries were congested. Another section of trachea, taken from a portion of the wall near the ulcer, bore stratified columnar epithelium and showed a similar cellular infiltration in the submucosa.

Mediastinal Node: The cells within the follicles were decreased in number. Small numbers of plasma cells were seen in the follicles. The reticulum in the remainder of the node was increased in amount, and plasma cells and a few polymorphonuclear leukocytes were seen here.

No significant abnormalities were seen in the spleen, liver, adrenal glands, kidneys, pelvic organs, gastrointestinal tract, thymus, pancreas, thyroid gland, skin, striated muscle or central nervous system.

Anatomic Diagnosis.—The diagnoses were congenital web of the larynx, operation (tracheotomy), granulation tissue above the tracheostomy, stratified squamous cell metaplasia of tracheal mucosa, chronic ulcer of the trachea, chronic aspiration pneumonia, hemosiderosis of the lungs, acute edema and hemorrhage of the lungs, vomitus in the larynx and trachea, dilatation of the right ventricle and tricuspid valve, congestion of the intestinal tract, chronic lymphadenitis, hyperplasia of the thyroid gland, accessory spleen, accessory adrenal gland, anomalous folds of esophageal mucosa and patent foramen ovale.

COMMENT

In 1942 McHugh and Loch[1] reviewed 133 cases of congenital laryngeal web. Most of these webs were typically wedge shaped, with a thin concave border posteriorly, and extended between the anterior portions of the true vocal cords. Of the cases in this review, in 75 per cent the web was at the level of the vocal cords. Only 1.5 per cent of the webs were supraglottic, and only 3.7 per cent of the webs (5 cases) extended to the posterior portions of the larynx. The size of the web was given in 108 cases. A small posterior opening with a large web over the remainder of the lumen was the least frequent finding (five cases).

The age of occurrence varied from 8 months (a premature infant) to 70 years. Twenty-three patients were up to 1 year of age, four from 2 to 10 years and 96 11 years or older. Other malformations were present in 11.3 per cent of the patients. The symptoms varied with the type and extent of web present. In infants the common complaints, in order of frequency, were (1) aphonia; (2) inspiratory and expiratory stridor, perhaps crowing; (3) difficulty in feeding; (4) dyspnea and cyanosis, sometimes suffocation with retraction, and (5) convulsions (rare).

In the nine cases of congenital laryngeal web encountered in Babies Hospital since 1932, including the present case, three patients were infants under 1 year of age and the other six children 1 to 11 years of age. In addition, there was one case of fusion of the vocal cords at their anterior margin, one case of a loose, flapping right ventricular band, and one case of a shortened aryepiglottic fold which limited the capacity of the larynx. Symptoms were present in all; they included alteration of the voice, which varied from weak and whispering to high pitched, hoarseness, stridor and dyspnea. Two of the webs were not adequately described; the others were thin and concave posteriorly and extended across the anterior one third or two thirds of the true vocal cords. Two of the nine patients had associated congenital anomalies.

The web in the case presented is of a rare type. It was supraglottic (1.5 per cent in McHugh and Loch's review) and extended to the posterior portions of the larynx (3.7 per cent in the same paper).

1. McHugh, H. E., and Loch, W. E.: Congenital Webs of the Larynx, Laryngoscope **52**:43, 1942.

Cases in reports published by Böcker,[2] Clerf,[3] Schmiegelow [4] and Kiaer [5] and Elsberg [6] resemble this case in that the webs were large with only a small posterior opening. However, all were between the true vocal cords instead of between the ventricular folds as in this patient. Two examples of webs between the ventricular folds were described by Zurhelle [7] and Clerf.[3] The first was thinner and smaller than the one in this case. The second was large but thin; it ballooned up with expiration. In reports of two cases [8] published since 1942 the abnormality described is quite different from the one in the present case.

The embryology of the larynx presents a possible explanation for the formation of such an anomaly.[9] The following description is a brief summary of the stages which are of interest here.

Toward the end of the first month of fetal development the branchial arches have grown ventrally and fused to form the floor of the future pharynx. Frazer describes the fifth arch mass as forming most of the larynx. It grows in the form of two lateral swellings, which press against each other to make a sagittal fissure, or gutter. These lateral masses continue to grow and press forward so that a transverse fissure is also formed at the cephalad end of the sagittal suture. These two lateral masses of the fifth arch fuse except for a small posterior opening at the end of the sagittal suture, which may remain patent. This is probably the origin of the small posterior opening in this case. The fifth arch mass then undergoes a general "dissolution," which begins from below with the formation of the cricoid cartilage and from above with the formation of the arytenoid cartilages. These two processes of dissolution normally meet at a level that would correspond to a line drawn along the true cords and up the medial margins of the arytenoid cartilages.

It appears, then, that in this case the process of dissolution was abnormal, and the final point of dissolution was higher than normal. However, the chordal nodule must have retained its normal position, since the small vocal cords are at their usual level.

The treatment of this child would certainly have been difficult. The prognosis for speech is questionable. The cords were present but were shorter than normal.

SUMMARY

A case of rare congenital web of the larynx is presented with a brief review of the literature and description of the embryology. A hypothesis is presented which provides a reasonable explanation of the formation of such an anomaly.

2. Böcker, A.: Ein seltener Fall von Kehlkopfstenose, Deutsche med. Wchnschr. **3**:193 and 205, 1877.

3. Clerf, L. H.: Congenital Stenosis of the Larynx: Report of 3 Cases, Tr. Am. Laryng. A. **53**:207, 1931.

4. Schmiegelow: Diaphragma congenitum laryngis, Zentralbl. f. Laryngol. **17**:276, 1901.

5. Kiaer, G.: Den kroniske larynxstenosis mekaniske behandling, Hosp.-Tid., Københ. **5**:457, 1897. This is the same case as that reported by Schmiegelow.[4]

6. Elsberg, L.: Report of a Case of Congenital Occlusion of the Rima Glottidis (One Case), Tr. A. M. A. **21**:217, 1870.

7. Zurhelle: Ein Fall von congenitaler Laryngostenose, Berl. klin. Wchnschr. **6**:544, 1869.

8. Poe, D. L., and Seager, P. S.: Congenital Laryngeal Web: Eradication, Arch. Otolaryng. **47**:46 (Jan.) 1948. Monteiro, A.: Diaphragma laryngis congenitum, Hospital, Rio de Janeiro **22**:545, 1942.

9. McHugh and Loch.[1] Frazer, J. E.: The Development of the Larynx, J. Anat. & Physiol. **44**:156, 1910.

SUDDEN DEATH OF A CHILD DUE TO CARDITIS

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REPORTS of sudden nonviolent death due to carditis in childhood are infrequent. Hence the following case is considered worthy of reporting. In this case the death was thought to be due to carditis of rheumatic origin.

REPORT OF CASE

A 2 year old girl, apparently well, died suddenly while at home. She was playing with her brother just before lunch and was running to pick up a book but unexpectedly fell. The brother attempted to help her, but she pushed him away. The mother, who was close by, lifted the child and noted that she was stiff and gray but still breathing in gasps. She hurried to the kitchen and attempted to revive the child by placing her under the cold water tap, but she died.

There were no significant past illnesses. Three weeks before the child's death two of the four other children had had colds. One week later the child was immunized against diphtheria and whooping cough and felt sick for a few days. About this time she had the end of her finger crushed in a door.

At autopsy the heart weighed 60 Gm. (normal, 56 Gm.), and the mitral and aortic valves were slightly opaque. Occasional petechiae were observed in the epicardium, and ecchymoses were present in the bases of both lungs. The thymus weighed 30 Gm. (normal, 23 Gm.), and there were no other remarkable findings. The gross examination revealed no definite cause for this puzzling death, and it was felt at the time that the cause might be related to the status thymicolymphaticus constitution.

Microscopic examination, however, revealed a pancarditis. In the myocardium there were interstitial and paravascular foci of inflammatory cells characterized by an infiltration of lymphocytes and histiocytes of the Aschoff type (figs. 1 and 2). There was fibroblastic proliferation in these zones, and an eosinophilic confluent fibrillar type of degeneration was noted in the connective tissue. Pale-staining cells in perivascular locations appeared at first to be degenerated muscle fibers, but special staining disclosed them to be fetal fat cells which were extending inward from the epicardium (fig. 3).

There was a myxomatous fibrous thickening of the mitral and aortic valves, and some of the collagen fibers were swollen, straight and deeply staining, undergoing fibrinoid degeneration (fig. 4). Collections of lymphocytes and histiocytes were scattered in the valves. There was subendocardial, as well as epicardial, fibrosis. Nothing else of significance was encountered microscopically.

The picture appeared to be one of rheumatic carditis, although other entities such as encephalomyocarditis[1] and hypersensitivity reaction were considered. The sudden death was

From the Department of Pathology (Wellesley Division), Toronto General Hospital.

1. Helwig, F. C., and Schmidt, E. C. H.: Science **102**:31, 1945. Pappenheimer, A. M.; Daniels, J. B.; Cheever, F. S., and Weller, T. H.: J. Exper. Med. **92**:169, 1950. Smadel, J. E., and Warren, J.: J. Clin. Investigation **26**:1197, 1947. Warren, J., and Smadel, J. E.: J. Bact. **51**:615, 1946; Fed. Proc. **7**:311, 1948.

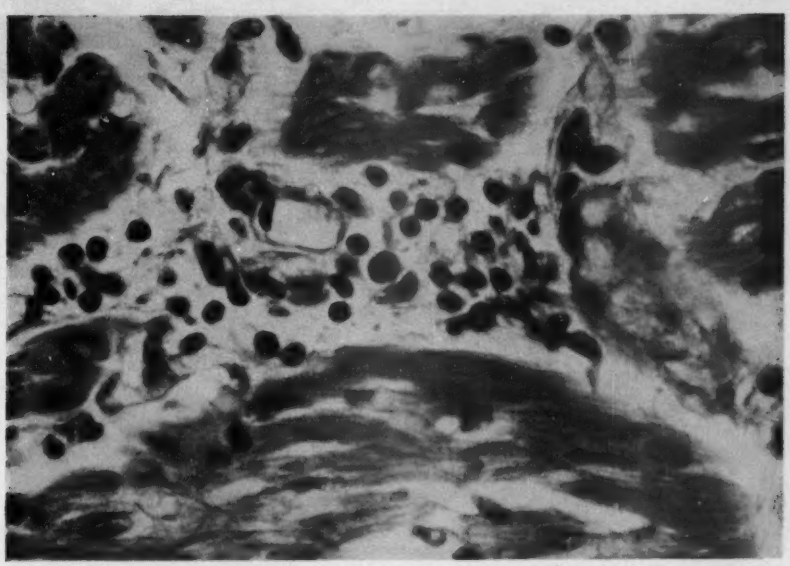

Fig. 1.—Myocardium showing paravascular infiltration of lymphocytes and histiocytes, with fibroblastic proliferation. Hematoxylin and eosin; × 430.

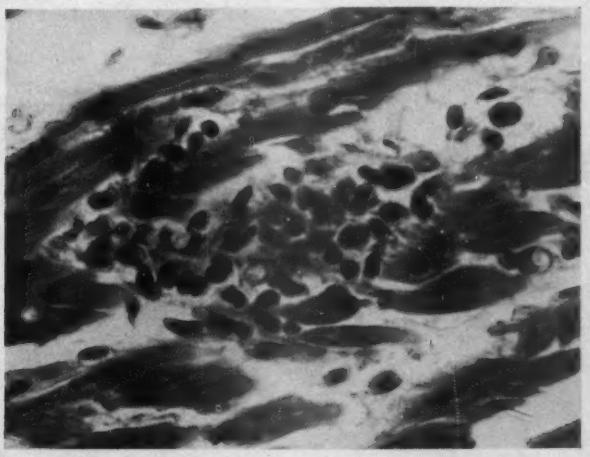

Fig. 2.—Myocardium showing a focal interstitial collection of lymphocytes and histiocytes. Hematoxylin and eosin; × 570.

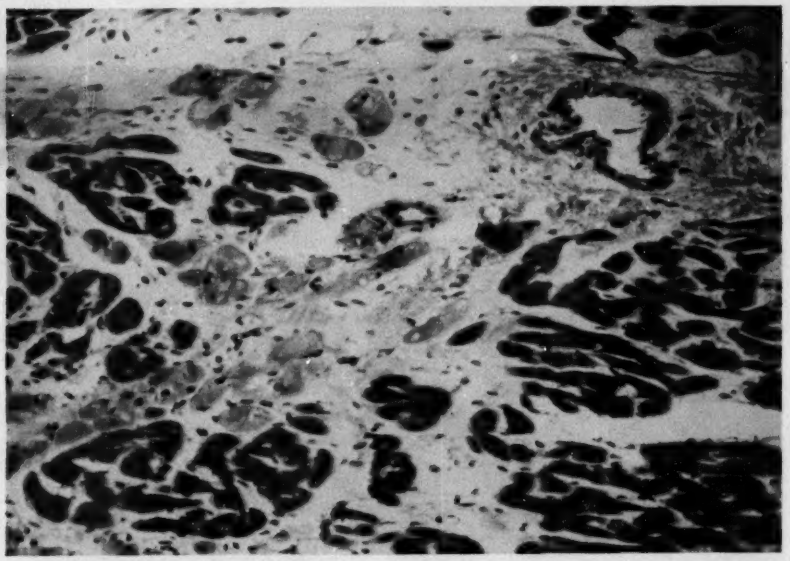

Fig. 3.—Myocardium showing fetal fat cells among muscle fibers and perivascular fibrous tissue undergoing degeneration. Masson connective tissue; × 74.

Fig. 4.—Mitral valve showing fibrinoid degeneration of collagen fibers and chronic inflammatory cell infiltration. Phosphotungstic acid hematoxylin; × 148.

attributed to the development of a cardiac arrhythmia or to myocarditis possibly causing ventricular failure or sinus arrest. Vagal stimulation may have been a factor in this case also.

COMMENT

Statistics concerning sudden nonviolent death deal mostly with adults.[2] Among this group the cardiovascular system [3] is most frequently involved, with coronary artery disease the most predominant cause of death.[4] Rheumatic carditis is not frequently mentioned as the cause of sudden death,[5] the reported percentages of heart disease deaths caused by it ranging from 2.5 [3d] to 9.8.[6]

In infancy the infectious diseases play an important part in the causation of sudden death. The respiratory infections are most frequently reported.[7] Congenital malformations are the next in consequence.[8] Rheumatic carditis is only rarely recorded.[9] The thymus is frequently implicated,[10] but the consensus is that it is not significant as a factor in sudden death.[11] Finally, it must be remembered that children have an exaggerated reaction in regard to fever, fluid balance, vitamin deficiency [7d] and hormonal imbalance.[12]

Sudden nonviolent instantaneous death is usually of cardiac origin.[13] More prolonged death comes from cerebral, pulmonic, abdominal, aortic or peripheral sources.[14] In the table one sees the mechanical effects on the heart and the

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2. (*a*) Bedford, T. H. B.: J. Path. & Bact. **36**:333, 1933. (*b*) Cleland, J. B.: M. J. Australia **1**:221, 1945. (*c*) Helpern, M., and Robson, S. M.: New York State J. Med. **45**:1197, 1945. (*d*) Helpern, M.: Tr. A. Life Insur. M. Dir. America **31**:131, 1947. (*e*) LeRoy, C. V., and Snider, S. S.: Sudden Death of Patients with Few Symptoms of Heart Disease, J. A. M. A. **117**:2019 (Dec. 13) 1941.

3. (*a*) Helwig, F. C., and Wilhemy, E. W.: Ann. Int. Med. **13**:107, 1939. (*b*) Magner, D.: Am. J. M. Sc. **198**:246, 1939. (*c*) Markowitz, B.: Illinois M. J. **76**:170, 1939. (*d*) Moritz, A. R., and Zamchek, N.: Sudden and Unexpected Deaths of Young Soldiers: Diseases Responsible for Such Deaths During World War II, Arch. Path. **42**:459 (Nov.) 1946. (*e*) Richards, R.: Brit. M. J. **2**:51, 1947. (*f*) Saphir, O.: Myocarditis: General Review, with Analysis of 240 Cases, ibid. **32**:1000 (Dec.) 1941. (*g*) Scott, R. W., and Simpson, M. A.: Tr. A. Am. Physicians **51**:375, 1936. (*h*) Weiss, S.: M. Clin. North America **23**:1323, 1939. (*i*) Bedford.[2a] (*j*) Helpern and Robson.[2c] (*k*) Helpern.[2d]

4. Cleland.[2b] Helpern and Robson.[2c] Helpern.[2d] Richards.[3e]

5. Griffith, G. C., and Huntington, R. W.: Ann. Int. Med. **25**:283, 1946.

6. White, P. D.: Heart Disease, ed. 3, New York, The Macmillan Company, 1946.

7. (*a*) Deadman, W. J.: Canad. M. A. J. **56**:273, 1947. (*b*) Goldbloom, A., and Wiglesworth, F. W.: Ibid. **38**:119, 1938. (*c*) Simpson, K.: Lancet **253**:745, 1947. (*d*) Woolley, P. V.: J. Pediat. **26**:572, 1945. (*e*) Richards.[3e] (*f*) Weiss.[3h] (*g*) White.[6]

8. Goldbloom and Wiglesworth.[7b] Richards.[3e]

9. Quinlan, J. T.: Brit. M. J. **2**:695, 1942. Hamilton, T. R.; Tanner, W. A.; Pebley, E. M. and Voorhees, G. S.: Am. J. Path. **24**:707, 1948.

10. (*a*) Archibald, A. C.: Arch. Pediat. **59**:57, 1942. (*b*) Boyd, W.: A Text-Book of Pathology, ed. 5, Philadelphia, Lea & Febiger, 1947. (*c*) The Thymus: A Symposium, Vancouver M. A. Bull. **20**:34, 1943.

11. (*a*) Simpson, K.: Lancet **256**:558, 1949. (*b*) Young, M., and Turnbull, H. M.: J. Path. & Bact. **34**:213, 1931. Footnotes 7 *b*, 2 *c* and 10 *c*.

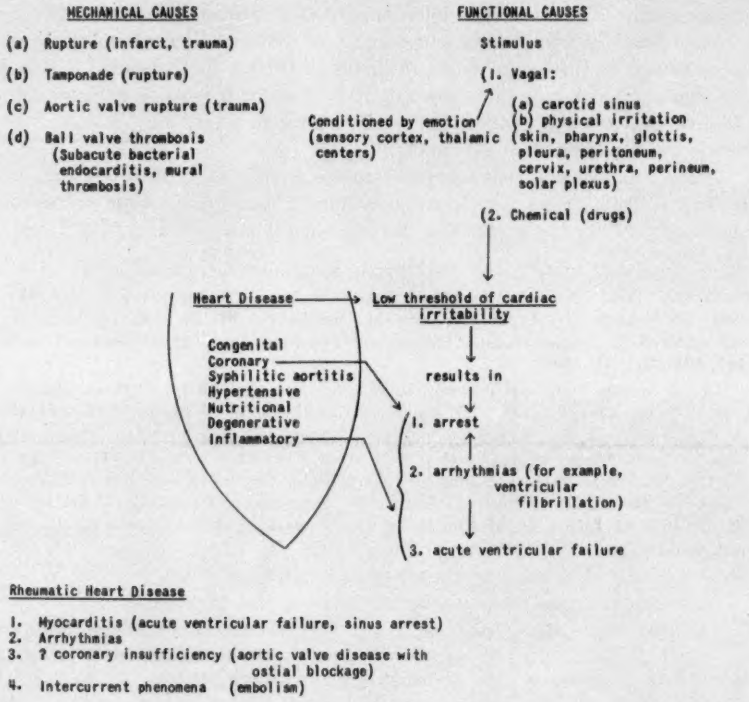
12. Provenzano, R. W.: New England J. Med. **242**:87, 1950. Simpson, K.: Lancet **232**:853, 1937.

13. (*a*) Levine, S. A.: Clinical Heart Disease, ed. 3, Philadelphia, W. B. Saunders Company, 1947. (*b*) Bedford.[2a] (*c*) Cleland.[2b]

14. Boyd.[10b] Levine.[13a]

resultant sudden loss of life. The functional causes are based on experimental, clinical and theoretical grounds. Any of the heart diseases mentioned produce a low threshold of cardiac irritability.[15] A stimulus acting on a heart with such a low threshold thus may produce arrest, any of the arrhythmias or acute ventricular failure. The stimulus is often of vagal origin and may be the result of a hyperactive carotid sinus or a lengthier reflex arc in which the afferent portion may

MECHANISM OF SUDDEN DEATH OF CARDIAC ORIGIN



come from skin, pharynx, glottis, pleura, peritoneum, cervix, urethra, perineum or solar plexus.[16] Vagal stimulation is conditioned by emotion, and a high degree

15. (*a*) Moritz, A. R.: New England J. Med. **223**:798, 1940. (*b*) Weiss, S.: Ibid. **223**:793, 1940.

16. (*a*) Best, C. H., and Taylor, N. B.: Physiological Basis of Medical Practice: A University of Toronto Text in Applied Physiology, ed. 2, Baltimore, William Wood & Company, 1939. (*b*) Gardner, E.: Med.-Leg. & Criminol. Rev. **10**:120, 1942; **11**:1943. (*c*) Hill, I. G. W.: Quart. J. Exper. Physiol. **22**:79, 1932-1933. (*d*) Laplace, L. B.: Internat. Clin. **1**:180, 1939. (*e*) Moritz.[15a] Simpson.[11a]

of anxiety, fear or the like facilitates the reflex.[15] In addition, heart disease directly may produce any of the cardiac irregularities listed.[16d]

In rheumatic heart disease the associated myocarditis may be followed by acute ventricular failure or sinus arrest, or an arrhythmia may ensue. It has been postulated that coronary insufficiency may be brought on by aortic valve disease with ostial blockage. Intercurrent phenomena such as embolism may lead to death, the latter being more prolonged (table).[16d]

SUMMARY

A case of sudden death in childhood is reported. Microscopic study revealed carditis thought to be of rheumatic origin. Causes of sudden death are reviewed briefly, and the mechanism is represented diagrammatically.

TREATMENT OF TOXIC DIFFUSE GOITER (GRAVES'S DISEASE) IN CHILDHOOD

Report of a Case Successfully Treated with Propylthiouracil

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In previous publications [1] it was pointed out that although surgery may be the best procedure in treating toxic diffuse goiter in adults, conservative management is recommended when the condition occurs before puberty. A report was given of eight children who had been treated medically and who after a follow-up period of from 3½ to 25 years were all entirely well.

The points in favor of the medical treatment of toxic diffuse goiter may be briefly summarized. 1. Operative mortality, although concededly low since the advent of iodine, is ever present, whereas no reports of death among medically treated children are to be found in the literature. 2. Even the most enthusiastic advocates of surgery admit that postoperative complications and sequelae are more frequent in children than in adults. Secondary hemorrhage, wound sepsis with extending mediastinitis, pneumonia, pulmonary collapse, postoperative tetany, postoperative crisis and laryngeal nerve injury with vocal cord paresis have been reported. 3. Postoperative hypothyroidism is frequent and, although easily controlled, may exact a greater penalty in the growing child than in the adult. The amount of thyroid tissue to be removed is still debatable, and one cannot predict the future needs of the developing organism. 4. Since the thyroid gland plays such an important role in growth and development, it seems advisable to avoid surgical removal whenever possible. 5. The thyroid gland is not the primary etiologic factor in this condition and its removal does not eliminate the cause; postoperative recurrences and persistent hyperthyroidism are fairly frequent.

As a matter of fact, thyroidectomy, even when most skilfully performed and with the best of results, cannot be the answer to the problem of a disease the cause of which is still uncertain. As Means [2] has aptly stated: "In the final analysis, surgical operation should be looked upon as ideal treatment only for purely mechanical conditions. It is impossible to conceive of a better treatment for, let us say, hernia, than surgical repair. It is quite possible, however, at least to imagine a form of treatment for toxic goiter, which will in some non-surgical fashion remove or render ineffective the primary cause of the disease."

This statement seems prophetic in the light of recent investigations, since such "a form of treatment which renders ineffective the primary cause of the disease"

From the Pediatric Service of Dr. Horace L. Hodes, Mount Sinai Hospital.

1. Topper, A.: J. Mt. Sinai Hosp. **1**:107, 1934; Treatment of Exophthalmic Goiter in Childhood: A Report of a Follow-Up Study in 12 Cases, Am. J. Dis. Child. **76**:26 (July) 1948; J. Am. M. Women's A. **4**:181, 1949.

2. Means, J. H.: The Thyroid and Its Diseases, Philadelphia J. B. Lippincott Company, 1937, p. 577.

has been found in the use of thiouracil and its related compounds.[3] These drugs block the synthesis of thyroxin. They have toxic effects, however, especially on the hemopoietic system. Propylthiouracil, which seems to be superior to thiouracil and less toxic, is being investigated in many clinics.[4] There is no uniformity of opinion as to whether these drugs should be used merely for preoperative preparation or for medical management of the disease. The drug used preoperatively has caused the mortality rate to be decreased to 0.1 per cent. Wagner[5] treated two children at the Peter Bent Brigham Hospital with propylthiouracil, and Wilkins[6] similarly treated six children at Johns Hopkins Hospital. Aside from these two reports, I could find no published reports in the literature of the use of this drug for children.

For this reason and in order to add support to the advocates of the conservative management of toxic diffuse goiter when it occurs before puberty, this paper is written to report a case in which the disease was successfully treated with propylthiouracil.

REPORT OF A CASE

S. H., an American girl of 11½ years, was admitted to the wards of the Mount Sinai Hospital on Sept. 22, 1947 with a history of weakness and a loss of 15 pounds (6.8 Kg.) in the preceding three months. There had been increasing restlessness, sweating of the hands and prominence of the eyes for the preceding six weeks. The child had complained of frequent supraorbital headaches.

Family History.—The father was a house painter who found it difficult to make both ends meet and was worried about his financial security. The mother was a psychoneurotic, who, by her own admission, spent more time at the various clinics than at home and who called herself "Mrs. Mount Sinai." A brother of the patient, aged 18, attended City College and was too concerned with his own problems to be of much help to the patient. The child was thus alone within her immediate family circle and found refuge in a large group of friends, with whom her difficulties seemed to be less marked than when she was at home.

The past history, except for the fact that the patient has been treated at the allergy clinic for the past five years, seemed to be irrelevant.

Ten days before admission the patient was seen in the outpatient department. Because of a pulse rate of 122, a widely increased pulse pressure (blood pressure 120/45) and the clinical symptoms of toxic hyperthyroidism, hospitalization was advised.

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4. Astwood, E. B., and Vanderlaan, N. P.: J. Endocrinol. **5**:424, 1945.

5. Wagner: Personal communication to the author.

6. Wilkins: Personal communication to the author. Astwood, E. B.: Bull. New England M. Center **7**:202, 1945. McCullagh, E. P.; Ryan, E. J., and Schneider, R.: Cleveland Clin. Quart. **13**:232, 1946.

Physical examination on admission showed a hyperactive preadolescent girl with extreme emotional instability. There was marked exophthalmos, with lid lag and impairment of convergence. There was left abducens weakness. The thyroid gland was symmetrically enlarged (fig. 1). There was a palpable thrill and an audible bruit over the gland. The heart was not enlarged. The heart sounds were normal, and there was a systolic murmur heard over the apical and basal areas. There was marked tremor of the extended hands. The child weighed 89 pounds (40.4 Kg.). The pulse rate was 122 a minute; blood pressure was 116/45 (pulse pressure 71).

Fig. 1.—Patient, aged 11½, shortly after admission to the hospital.

Laboratory Data.—An electrocardiogram showed a simple sinus tachycardia of 110. Roentgenograms showed the long bones to be normal. A roentgenogram of the chest showed no pathologic condition in the lungs. The pulmonary artery segment was conspicuous. Basal metabolic rate was + 35 per cent. The glucose tolerance was normal. Blood examination showed a hemoglobin level of 12 Gm., a red cell count of 4,370,000 and a white cell count of 5100 with 46 per cent polymorphonuclears, 49 per cent lymphocytes and 5 per cent eosinophils. The urine was normal. The blood chemistry was normal. The cholesterol was 200 mg. per 100 cc. Creatine was 165, creatinine, 835 in 750 cc. of urine. Exophthalmometric readings were 22 mm. for the right eye and 21 mm. for the left eye.

Course in the Hospital.—After two weeks of bed rest, high calory, high carbohydrate, high protein and high vitamin diet, with sedation, there was no apparent change. The child was referred to the psychiatrist, who found that she had had a marked emotional conflict with her mother which had apparently caused psychically traumatic situations in the home. Because of the marked restlessness, it was decided to allow the patient to get out of bed. She was given propylthiouracil, 50 mg. twice a day, together with psychotherapy. After four weeks on this regimen, the basal metabolic rate dropped to + 8 per cent, the pulse rate, to 90 and the

Follow-Up History of Patient with Toxic Diffuse Goiter Treated with Propylthiouracil

Date	Weight, Lb.	Height, In.	B.M.R., %	Pulse	Blood Pressure	Therapy*	Comment*
12/11/47	104	59¼	+8	90	106/66	100 mg. propylthiouracil; psychotherapy	Palms moist; tremor; marked exophthalmos
1/21/48	106	....	...	92	100/60	Unchanged	Child allowed to return to school
2/24/48	108½	....	...	88	100/62	50 mg. P.; sedatives as needed	Doing well at school; carrying a full P.T. program
3/24/48	110	60	...	80	90/60	Unchanged	Practically no symptoms
4/14/48	112½	....	—2	76	92/68	Stop drug because of low w.b.c. and B.M.R.	W.b.c. 4,600; exophthalmos marked
5/12/48	113¼	....	...	80	90/60	No drugs	W.b.c. 5,700; symptom free
6/26/48	113½	....	...	80	92/64	No drugs	Advised to go to summer camp
During July and August the child was at camp participating in all activities. Did very well. First menstrual period appeared August 16.							
9/15/48	116½	61½	+4	82	92/60	Psychotherapy resumed; no drugs	W.b.c. 7,100; symptom free; exophthalmos marked
11/10/48	122	....	...	88	100/60	No drugs	Doing very well
12/16/48	115	....	...	100	100/60	P. 50 mg. and sedatives resumed; psychotherapy	3 day history of vomiting and exacerbation of symptoms after quarrel with mother
12/23/48	...	....	...	90	90/60	Unchanged	Child much quieter
1/26/49	118	....	...	86	92/62	P. reduced to 25 mg.	Second menses Jan. 10
2/23/49	120	62	—5	76	90/60	Stop drugs because of low w.b.c. and B.M.R.	W.b.c. 4,500; symptom free; exophthalmos improved
4/ 6/49	121¼	....	...	80	92/62	No drugs	W.b.c. 6,500; menses regular since 1/10
6/ 1/49	125¼	....	...	80	90/60	No drugs	Symptom free
6/22/49	127¼	....	...	..	.....	No drugs	Advised to go to camp
9/ 7/49	127½	63	+9	86	90/60	No drugs; psychotherapy resumed	In excellent health; menses regular
11/ 2/49	129	....	...	82	100/70	No drugs	W.b.c. 6,700; symptom free; slight exophthalmos
1/11/50	130	....	...	76	98/68	No drugs	Has no time to attend child guidance clinic
3/10/50	131¼	63½	+8	78	96/66	No therapy	Was graduated from high school
5/10/50	131½	....	...	78	90/60	No therapy	Symptom free; no exophthalmos O.D. 19 O.S. 19

* Abbreviations used in the table: P, propylthiouracil; w.b.c., white blood cell count; P.T., physical therapy; B.M.R., basal metabolic rate; O.D., exophthalmometric reading for the right eye, and O.S., for the left eye.

blood pressure, to 90/60. The child was considerably quieter. She gained 6½ pounds (2.9 Kg.) during this period.

The child was discharged as improved on Nov. 21, 1947, after two months of hospitalization. Her weight was 99 pounds (44.9 Kg.). She was referred to the growth and development clinic for further observation.

Follow-Up History (table).—The patient is now 14½ years old. During the follow-up period of two years and six months (from Nov. 21, 1947 to May 10, 1950) the patient had gained 32½ pounds (14.7 Kg.) and grown 4½ inches (11.4 cm.). All the symptoms of hyperthyroidism gradually disappeared; now all are entirely gone.

The exophthalmos was the last symptom to disappear. The menses are regular. The situation at home is unchanged, but the patient says, "It doesn't bother me any more." The patient is considered cured (fig. 2).

Fig. 2.—Patient, aged 14½, after being graduated from junior high school.

COMMENT

There is probably no other disease that can be as truly labeled "psychosomatic" as toxic diffuse goiter. Attention has been called again and again to a psychogenic factor in the pathogenesis of this condition. As early as 1922 Hyman, Lieb and

Kessel [7] reported psychic trauma preceding the onset of symptoms in 72 per cent of their cases of toxic diffuse goiter. In studying the past history of 200 patients with this condition, Conrad [8] found obviously disturbed mother-child relations which appeared to have precipitated the syndrome or to have brought about an exacerbation of symptoms.

In the case here reported, there was continuous conflict between the patient and her psychoneurotic mother, which may well have precipitated the onset of symptoms. Again, after the child had been symptom free without drugs for about seven months, an exacerbation of symptoms was brought about by quarrels with the mother over a crippled boy whom the patient was befriending. At this time the child was anxious to overthrow her childhood dependence but was yet too young to integrate her own personal life. The resulting conflict brought about anxiety and imbalance of hormonal secretion. Fortunately, the patient was being treated by an understanding psychiatrist, and this, together with the help of propylthiouracil over a short period, helped tide over a difficult period.

The absence of symptoms without any medication for the past 14 months, during which time the child attended high school regularly and participated in extracurricular activities—all this in the face of an unchanged situation at home—speaks for the arrest of the disease in this patient. That such spontaneous arrest of symptoms usually coincides with the establishment of puberty, as it did in this case, has already been pointed out in the eight cases previously reported.

With the advent of propylthiouracil it is quite possible that toxic diffuse goiter when it occurs before puberty will become a problem of internal medicine alone. We know that propylthiouracil produces remissions. Whether these remissions are temporary or permanent, time alone will tell. The important thing is to bring about remission of symptoms until puberty brings about a spontaneous arrest of the disease. That this should occur during puberty is understandable. At that time there is a change in endocrine activity. The role of the gonads assumes greater importance, that of the thyroid gland, less importance, as the needs for somatic growth become subordinate to the needs for maturation.

It is known that even adults with toxic diffuse goiter often show a tendency toward spontaneous recovery. If this is true of the catabolic metabolism of the adult, it should certainly be true of the dynamic, anabolic metabolism of the young organism in whom constructive and regenerative tendencies are dominant. Consequently, when toxic diffuse goiter occurs before puberty, it seems logical to treat it conservatively whenever possible.

Conservative management includes rest, proper diet with adequate vitamin intake, sedatives where indicated, psychotherapy and, as needed, some antithyroid drug.

No discussion of the treatment of toxic diffuse goiter would be complete without a word about radioactive iodine. This substance causes remissions in the disease. Whether it is equal to or better than treatment with antithyroid drugs is not yet established, since the patients receiving radioactive iodine for toxic goiter have not been followed long enough to warrant conclusions concerning the percentage of permanent cures or the evidence of complications.

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7. Kessel, L.; Lieb, C. C., and Hyman, H. T.: A Study of Exophthalmic Goiter and the Involuntary Nervous System: An Estimation of the Pathogenesis and the Evaluation of the Therapeutic Procedures in Exophthalmic Goiter, J. A. M. A. **79**:1213 (Oct. 7) 1922.

8. Conrad, A.: J. Nerv. & Ment. Dis. **79**:505 (May); 656 (June) 1934.

The therapeutic effect of radioactive iodine is probably due to destructive action on the parenchymal cells; consequently, further knowledge of the minimal dose that will control the disease without destroying too much functioning tissue is required before this substance can be used safely in children.

Because of this fact, and because of the existing uncertainty as to the possibility of late carcinogenic action and a possible damaging effect on the kidneys during excretion, many investigators believe that this substance should be reserved for patients 45 years of age or over and for adults who are poor surgical risks.

At present the drug of choice, at least for children, seems to be propylthiouracil. Whether this will be succeeded by some other as yet undiscovered compound is unimportant. The important consideration is to avoid surgery.

Abstracts of Current Literature

Newborn

From Birth to Walking: Studies on Some Modes of Activity of the Newborn. André-Thomas and F. Hanon, Presse méd. **56**:229 (March 31) 1948.

The authors collaborated on a film stressing the precocious development of standing and walking in the newborn infant. If the newborn is supported in an upright position with the feet in contact with a table and the body pushed forward, the legs will begin a rhythmical alternate forward movement similar to mature walking.

They also explain the mechanism of the first breath. As the body is withdrawn from the vagina, the arms are at first relaxed, then actively abducted as the head is extended, and a breath is taken. This, they point out, is similar to one method of artificial respiration.

The film also demonstrates the Moro reaction produced by abrupt extension of the head and neck on the trunk, the Moro reaction produced by lifting the legs and suddenly pulling the legs and body toward the examiner, the nuzzle reflex, the curving of the trunk toward the stimulation when the lumbar region is pricked and the movement of a leg toward the point of stimulation when the opposite leg is extended and the sole stimulated.

Daffinee, Melrose, Mass.

Bronchial Obstruction in the Newborn. L. de Robert, Presse méd. **56**:444 (June 23) 1948.

Systematic examination of the lungs of babies stillborn or dying shortly after birth shows that intrauterine respiratory movements fill the bronchial tree and the alveoli with amniotic fluid and also with meconium, vernix caseosa and desquamated epithelial cells. These solid elements are sufficient to produce bronchial obstruction and fatal asphyxia. Photomicrographs are presented which show such obstructions.

Daffinee, Melrose, Mass.

The Significance of the Rh/rh Blood Group System for the Practice of Medicine. Peter Dahr, Schweiz. med. Wchnschr. **79**:613 (July 9); 646 (July 16) 1949.

In order to obviate transfusion accidents it is necessary to test the blood of donor and recipient with a standard anti-D serum (anti-Rh_0). The nomenclature of Fisher as well as of Wiener is used. (In the table under the heading "Genotyp [Genomosaik]" the English and American nomenclatures are transposed.) By testing with anti-D serum, in 90 per cent of the patients all Rh-conditioned transfusion accidents can be avoided. This also holds true for erythroblastosis. The remaining 10 per cent of the patients have to be tested for further Rh subgroups, with due regard to blocking antibodies.

Amberg, Rochester, Minn.

Exsanguination Transfusion by Way of the Upper Umbilical Vessels in Hemolytic Diseases of the Newborn. Pierre Gautier, Jean Guinand-Doniol and Francois Thelin, Schweiz. med. Wchnschr. **79**:711 (Aug. 6) 1949.

In three infants the exsanguination transfusion was done according to Pinkus with utilization of that portion of the umbilical vein which lies in the abdominal wall.

Amberg, Rochester, Minn.

Anatomic Pathogenic Considerations in Three Cases of Sclerema of the Newborn. Bruno Garau, Ann. ital. di pediat. **2**:119 (April) 1949.

Having anatomically studied three cases of sclerema neonatorum, Garau discusses the pathogenesis of this disease which is considered a clinical syndrome with various anatomic changes according to various determining causes.

From the Author's Summary.

THE METABOLISM OF IRON IN OBSTETRICS AND GYNECOLOGY. E. L. CUSTO and A. MUZIARELLI, Arch. ital. pediat. e puericolt. **12**:321, 1948.

The authors present a study concerning the amount of iron contained in the blood serum of the cord and in the peripheral blood serum of the newborn during the first 10 days of extrauterine life. The ratio between the amount of iron in the serum and the iron contained in the maternal blood and milk is examined.

This research is connected with the present knowledge of requirements regarding the metabolism of iron in the organism of the fetus. Studies were made regarding the passage of this metal from mother to fetus during prenatal life (through the placenta) and from mother to newborn during extrauterine life (by means of breast milk).

FROM THE AUTHORS' SUMMARY.

THE MATERNAL AGGLUTININS IN HOMOSPECIFIC AND HETEROSPECIFIC PREGNANCIES. F. FORTUNATO and B. RONDININI, Clin. pediat. **32**:29 (Jan.) 1950.

In heterospecific pregnancies, the titer of the maternal blood group specific agglutinins was found to be higher than in homospecific pregnancies.

HIGGINS, Boston.

GINGIVAL MYOBLASTOMA IN THE NEWBORN. E. SORAGNI and M. LOVINO, Lattante **20**:24 (Jan.) 1949.

A newborn infant was noted to have a kidney-shaped tumor the size of a large almond attached by a pedicle to the upper jaw in the region of the left incisors. The tumor was removed and studied histologically. A diagnosis of myoblastoma of Abrikossoff was made. Some authors have classified these tumors as congenital epulis.

HIGGINS, Boston.

MASTITIS OF THE NEWBORN TREATED AND CURED BY LOCAL AND GENERALIZED ADMINISTRATION OF PENICILLIN. S. MALANDRINO, Lattante **20**:32 (Jan.) 1949.

In a newborn female infant an abscess of the right breast developed on the twenty-fourth day of life; at birth, the labor had been difficult, and the Schultze method of resuscitation had been used. The abscess was aspirated and 30,000 units penicillin instilled on each of three days. Also 310,000 units of penicillin was given intramuscularly during this period. No report is given as to the bacteriology. The trauma at birth and the physiological stimulation of mammary secretion seem to have played a role in causing the abscess to form.

HIGGINS, Boston.

PHYSIOLOGICAL PECULIARITIES OF THE NEONATAL PERIOD. L. AURICCHIO, Lattante **20**:257 (May) 1949.

Observations in the Pediatric Clinic in Naples indicate that icterus neonatorum is due to an excretory defect in the liver. The physiological loss of weight of the newborn is due to a peculiar alteration in the permeability of the renal tissues and other tissues and expresses a transition in the physiological functions from fetal life to extrauterine activities.

HIGGINS, Boston.

ASTHMATIC REACTION IN THE NEWBORN. ALFREDO WIEDERHOLD, Rev. chilena de pediat. **19**:264 (March) 1948.

Weiderhold reports a case of asthmatic reaction in a newborn infant.

FROM THE AUTHOR'S SUMMARY.

GRAVE ANEMIA OF ERYTHROBLASTOTIC NEWBORN IN THE PREMATURE. J. A. FALCONI VILLAGÓMEZ, Rev. ecuator. pediat. **1**:132 (Sept. 22) 1949.

The case of a twin 1 month old and with a weight of 4 pounds who was born by cesarean operation because of antecedent placenta is reported. The other twin had died of jaundice four days after birth. It was the first childbirth of the mother. The child we attended

also suffered from jaundice, edema of the extremities and enlargement of the liver and spleen in connection with great malnutrition. It presented overlapping of the skull bones, cyanosis of the face and extremities and hypothermia.

The examination of the blood revealed a large quantity of erythroblasts and scarcely 700,000 red blood cells. Five intravenous transfusions were given and reticulogen,® nikethamide (coramine®) and vitamin K were injected; sulfadiazine was given orally. By this treatment the red blood cells increased to 3,600,000. Circulation became normal, and in two weeks the twin gained 1 pound. A wetnurse fed the child. One month after the first examination it was discharged, completely cured and weighing 7 pounds. FROM THE AUTHOR'S SUMMARY.

Acute Contagious Diseases

REDOXON THERAPY IN PERTUSSIS. LUCIE PFEIFFER, Helvet. paediat. acta **2**:106 (Jan.) 1947.

Success of vitamin C therapy for children with whooping cough could not be shown by alternate administration of the drug to children with the disease, neither in uncomplicated cases nor in those with complications. Research among monozygotic twins confirms the lack of success of vitamin C therapy in whooping cough. FROM THE AUTHOR'S SUMMARY.

ACTIVE DIPHTHERIA IN IMMUNIZATION IN TUBERCULOUS CHILDREN. E. MARTENS, Helvet. paediat. acta **5**:95 (March) 1950.

The stand of several authors for and against active immunization of tuberculous children against diphtheria is briefly discussed.

In view of the fact that no deterioration of the existing tuberculosis was observed by this author in 186 children with pulmonary and extrapulmonary tuberculosis, active immunization against diphtheria is recommended for tuberculous as well as nontuberculous children, especially children in sanatoriums. FROM THE AUTHOR'S SUMMARY.

EXPERIENCES WITH DIPHTHERIA: CRITICAL REMARKS ON THE PAPER BY RÖESGEN. K. SOEHRING, Schweiz. med. Wchnschr. **79**:38 (Jan. 15) 1949.

The paper of Röesgen gives as one of its conclusions that 11 to 14 year old children who were immunized against diphtheria are more likely to succumb to the after-effects. The author states that there is no statistical justification for such a conclusion.

AMBERG, Rochester, Minn.

HEMATOLOGIC SULFONAMIDE REACTIONS IN MEASLES. H. BRIEGER, Arch. f. Kinderh. **134**:65, 1947.

Sulfonamide medication during measles has no demonstrable influence on the total number of leukocytes. However, the percentage of lymphocytes increases and simultaneously the percentage of granulocytes decreases much faster in patients to whom sulfonamides are given than in untreated control patients. The "crossing of the leukocytes," i. e., the point at which the percentage of the lymphocytes becomes greater than the percentage of granulocytes, is observed in untreated controls around the seventh day; while in patients under sulfonamide medication this "crossing" takes place as early as the second or third day, at a time that the exanthem of measles is still present.

Sulfonamide medication during the incubation or prodromal stage of measles does not influence these stages or the later reaction during the measles period. Sulfonamides also do not change, clinically or hematologically, the course of an otitis which may accompany measles.

ARON, Chicago.

INVESTIGATIONS ON THE FUNCTION OF THE COMPLEMENT IN THE BLOOD OF DIPHTHERIA PATIENTS. J. STRÖDER and J. HÄSELER, Arch. f. Kinderh. **134**:80-92, 1947.

Determination of the complement titer in the blood of 85 children and adults with diphtheria revealed that the amount of complement in the blood during diphtheria, irrespective of the degree

of severity, is almost in all cases equal to the amount found in normal blood. Decrease of the complement or vanishing of the complement is very rare in diphtheria. Not in one case of toxic diphtheria, not even in the fatal ones, was this phenomenon found.

ARON, Chicago.

TOXOID THERAPY FOR DIPHTHERIA. J. CREMER, Arch. f. Kinderh. **134**:106, 1947.

The use of diphtheria toxoid instead of or in combination with antitoxin is definitely a new therapeutic procedure. This method is based on the following idea: The body cells may accept either toxin or toxoid. Toxin is dangerous; toxoid is not. If it would be possible to bring the toxoid to the body cells before the cells are reached by the toxin, the cells might be blocked against the toxin and thus be protected. To achieve this blockade the toxoid was given intravenously daily for ten consecutive days.

In Cremer's district of Western Germany diphtheria for some time has been developed from a children's disease into a disease more frequently seen in adults. During the spring of 1946, for every 50 cases in persons under 17 years of age, 360 cases in persons over 17 years of age were reported. Myocarditis is the most frequent complication of diphtheria in persons over 17 years of age. Therefore, continuous electrocardiogram control is required, even starting before toxoid therapy is initiated. Cremer has treated 95 persons with the new toxoid therapy. Of these, 60 remained free of myocardial damage and 35 showed some signs of damage in the electrocardiogram. None of the 95 toxoid-treated patients died, while a mortality of 4 to 5 per cent would have been expected without the use of toxoid (with antitoxin only).

ARON, Chicago.

THERAPY OF POLIOMYELITIS. LEONHARD VOIGT, Med. Klin. **44**:1129 (Sept. 2) 1949.

Two boys 5 and 8 years of age were taken ill acutely during an epidemic of poliomyelitis. They were regarded as having poliomyelitis in the preparalytic stage. Each received 6 to 7 ml. of their mother's blood subcutaneously or intramuscularly in the gluteal region, with rapid and excellent results. Since a large number of persons are infected without showing of symptoms, it may be assumed that the people in the vicinity of a patient and particularly those taking care of the patient "made acquaintance" with the virus, which probably caused it to become modified. It has been shown that experimental animals infected with virus cerebrally do not get sick if shortly after the infection a weakened virus is given intramuscularly. This is the so-called interference phenomenon. The treatment has to be given as early as possible and before paralysis sets in. It is entirely different from the treatment with reconvalescent blood.

AMBERG, Rochester, Minn.

TREATMENT OF SCARLET FEVER WITH PENICILLIN. A. HERRLICH, Med. Klin. **44**:1285 (Oct. 7) 1949.

Alternate patients of 252 patients with scarlet fever were treated with penicillin. The conclusion is reached that routine treatment in cases of light and moderately severe scarlet fever is not to be recommended. When treatment is given too early, the progress of immunity is disturbed without late complications being prevented, even though hemolytic streptococci are no longer found in smears. But in all cases of severe disease penicillin treatment is of value.

AMBERG, Rochester, Minn.

USE OF CIRCULATION REMEDIES IMPROVING THE BLOOD FLOW IN THE TREATMENT OF POLIOMYELITIC PARESIS. V. Klare, Wien. klin. Wchnschr. **61**:137 (March 4) 1949.

Priscoline® is the hydrochloric acid salt of 2 benzyl-4,5-imidazoline, related in constitution and action to histamine. It acts primarily on the arterioles and small arteries. It was administered in intramuscular depots, 10 to 20 mg. being divided among 2 to 3 depots. It was used in 45 cases of poliomyelitic paresis in children and youths. The skin temperature of corresponding areas was measured. In 4 per cent the elevation fell below 1 C. (38.8 F.). In 42 per cent it measured between 1 and 2 C. (35.6 F.), and in 54 per cent it exceeded 2 C.

In the latter cases a definite motor improvement was noted. Improvement of blood flow and motility persisted from six to 24 hours. In addition, an increased muscle tone was registered in these cases. With electrophoresis—5 to 10 per cent 2 benzyl-4,5-imidazoline solution at the anode—similar results were obtained. As early as at 2½ to three minutes, dilatation of the arterioles could be seen. The medication can be used alone or in combination with other methods of physical medicine.

AMBERG, Rochester, Minn.

GOEBEL'S REACTION. J. TAMÁSI, Paediat. danub. **2**:128 (Aug.-Sept.) 1947.

Goebel's phenomenon was observed in two children who received prophylactic doses of mother's blood to protect them from measles. One was given 40 cc. of blood on the fifth day of the incubation period. On the ninth day the area around the injection site became swollen, hard and sensitive, and the inguinal glands were also swollen. Fever and local symptoms subsided in another five days. On the fourteenth day measles exanthem appeared, with slight catarrhal symptoms and a temperature of 38 C. (100.5 F.).

In the other child, who also received 40 cc. of blood but on the fourth day of the incubation period, the reaction appeared on the eleventh day but was lighter than in the first patient. Measles did not develop.

The phenomenon is, according to Goebel, due to the simultaneous effect of virus and antibody. As the reaction could be observed only following inoculations made with whole blood, it is probable that blood corpuscles are responsible for it. It is not known whether their presence simply somehow hinders the absorption of serum containing antibodies or whether their action is a direct result of having formed some connection with the virus itself.

FROM THE AUTHOR'S SUMMARY.

DISSOCIATION ALBUMINOCYTOLOGICAL WITH CASES OF SEROUS MENINGITIS. L. BARTA and GERLOCZY, Paediat. danub. **2**:216 (Oct.) 1947.

Several cases of serous meningitis were observed. They were thought to be of poliomyelitic origin, as they occurred during an epidemic and displayed a course characteristic of that disease. Even flaccid paralysis occurred in 1 of the cases.

There was an unusual finding common in all the cases, a characteristic albuminocytological dissociation. In poliomyelitis, invariably pleocytosis occurs in the early stage and the protein content of the cerebrospinal fluid is mostly found to be in relation to the number of cells.

It is probable that there are connections between poliomyelitis and the syndrome of Guillain and Barré. According to the above observations, a high protein content of the cerebrospinal fluid with a low blood cell count may occur in both the early and the late stages of poliomyelitis.

FROM THE AUTHORS' SUMMARY.

MEASLES IN THE COURSE OF SCARLET FEVER. VACLAV KREDBA, Pediat. listy **4**:146, 1949.

When measles occurs together with scarlet fever in the acute stage, there is a summation of the two exanthems and the course of the disease is serious, with frequent complications. In the allergic stage the course of measles is atypical, with few catarrhal symptoms and without exanthem and Koplik spots. The exanthem is atypical. In the convalescence stage of scarlet fever the course of measles is typical.

FROM THE AUTHOR'S SUMMARY.

COMPLICATIONS OF SCARLET FEVER IN OSLO DURING THE PERIOD 1890-1947. HELGE B. GRANRUD, Acta paediat. **37**:163, 1949.

The frequency of deaths, relapses and complications from scarlet fever during three epidemics in Oslo in the years 1890-1947 has been investigated; in all, there were 5,100 cases. Mortality and relapses have decreased at an equal rate, the mortality from 7.8 to 0.0 per cent and the relapses from 5.8 per cent in 1937 to 0.4 in 1947. The frequency of complications has decreased only with regard to the cardiac complications and nephritis. The material indicates that during these years the frequency of the other complications has remained high up to the introduction of penicillin, in spite of the fact that the primary course has apparently been milder.

FROM THE AUTHOR'S SUMMARY.

Acute Infectious Diseases

HUMAN INFECTIONS CAUSED BY LACTOBACILLI. E. BIOCCA and A. SEPPILLI, J. Infect. Dis. **81**:112 (Sept.-Oct.) 1947.

From two fatal cases of sepsis with endocarditis a micro-organism has been repeatedly isolated whose bacteriologic characteristics are similar to those of Lactobacillus acidophilus, from which it should constitute a special variety (L. acidophilus pathogenes Biocca and Seppilli, 1944), as suggested in a previous publication.

In regard to pathogenicity, the authors are inclined to believe, on the basis of the results of experimental inoculations in mice and in chicken embryos, that their strains are endowed with a moderate virulence and that the clinical severity of the reported cases depended on the special localization, perhaps on previously damaged cardiac valves, and not on invasiveness or toxicity.

TOOMEY, Cleveland.

ROCKY MOUNTAIN SPOTTED FEVER TREATED WITH CHLORAMPHENICOL AND AUREOMYCIN. WILLIAM A. REILLY and A. M. EARLE, J. Pediat. **36**:306 (March) 1950.

In 6 cases Rocky Mountain spotted fever responded promptly to treatment with chloramphenicol or aureomycin.

MACDONALD, Pittsburgh.

TYPHOID AND PARATYPHOID FEVER: A REVIEW OF FOUR CASES TREATED WITH CHLOROMYCETIN.® MCLEMORE BIRDSONG, JOE E. MITCHELL and WILLIAM W. WADDELL, J. Pediat. **36**:310 (March) 1950.

Chloramphenicol (chloromycetin®) rapidly cured 3 patients with typhoid and 1 with paratyphoid. The authors suggest that when the drug is given early in the disease an immune response, as demonstrated by the Widal tests, may fail to develop. Patients not having acquired immunity might be subject to early reinfection.

MACDONALD, Pittsburgh.

TYPHOID FEVER IN AN INFANT COMPLICATED BY TYPHOID MENINGITIS. HOWARD W. RIPY, J. Pediat. **36**:376 (March) 1950.

In an infant with typhoid, typhoid meningitis developed and bacteremia continued while she was receiving chloramphenicol (chloromycetin®). She recovered promptly when aureomycin was given with the chloramphenicol.

MACDONALD, Pittsburgh.

OBSERVATIONS REGARDING ARTIFICIALLY INDUCED SUBCUTANEOUS NODULES IN RHEUMATIC FEVER PATIENTS. BENEDICT F. MASSELL, WILLIAM B. COEN and T. DUCKETT JONES, Pediatrics **5**:909 (June) 1950.

Subcutaneous nodules which are indistinguishable from spontaneously occurring nodules have been artificially induced in rheumatic patients by the subcutaneous injection of blood.

The frequency, size and duration of the induced nodules correlated closely with the severity and duration of the rheumatic process. Only infrequently could nodules be induced in control subjects suffering from conditions unrelated to rheumatic fever.

Although citrated blood obtained from patients with highly active rheumatic fever seemed to be more effective in inducing nodules in quiescent and mildly active rheumatic patients than did the patient's own blood, the active rheumatic blood was not more effective than blood obtained from healthy young adults.

The daily injection of convalescent rheumatic serum into the site of the nodule test did not interfere with the induction of nodules. Saline, as well as blood, effectively induced nodules in certain patients, provided that it was injected with the standard traumatizing technic.

It is concluded that the development of nodules results from injury to the subcutaneous fibrous tissue, the reactivity of which is altered by the rheumatic process, and that the hypothesis of a nodule-stimulating substance present in the blood of active rheumatic patients is untenable.

Nodules have been induced in some rheumatic patients by the subcutaneous injection of hyaluronidase. These observations, together with the observations of others that trypsin is also an effective nodule-inducing agent, suggest that enzymes may play a role in the mechanism of nodule formation. However, it is also possible that these substances act in quite a non-specific way and set off the nodule reaction merely by injuring the subcutaneous fibrous tissue.

FROM THE AUTHORS' SUMMARY.

THE RECOGNITION OF SUBSIDIARY FACTORS IN THE ETIOLOGY OF INFECTIOUS DISEASES. REGINALD LOVELL, Proc. Roy. Soc. Med. **43**:1 (Jan.) 1950.

Various factors and theories related to epidemiology and immunology of infectious diseases are described. Further methods of investigation dealing with causes are outlined. The means by which the potential pathogens commonly found are converted into epidemic strains capable of inducing infection is still unknown.

HEARD, Monterey, Calif.

SULFONAMIDE PROPHYLAXIS IN CONVALESCENT RHEUMATISM. GEOFFREY DE CRESPIGNY, Clin. Rep. Adelaide Children's Hosp. **1**:139 (Nov.) 1948.

Results observed in 43 cases of rheumatic fever in which 0.5 Gm. sulfamerazine was given twice daily indicate that this treatment is of distinct value. No child was readmitted with recurrence or reinfection, and untoward effects were rare. It is advised that this treatment be continued for five years in each case.

MCGUIGAN, Evanston, Ill.

A CASE OF KALA AZAR. R. L. THOROLD GRANT, Clin. Rep. Adelaide Children's Hosp. **1**:141 (Nov.) 1948.

A case of kala azar in a 3½ year old Greek immigrant is reported by Grant.

MCGUIGAN, Evanston, Ill.

SOME ASPECTS OF INFECTION. ERIC B. SIMS, Clin. Rep. Adelaide Children's Hosp. **1**:160 (Nov.) 1948.

The subject of infection is discussed from the historical aspect, with some of the infecting agents themselves briefly described and the modes by which they can infect the body tabulated and illustrated.

MCGUIGAN, Evanston, Ill.

GANGOSA IN A BOY. K. D. LAHIRI, Indian J. Pediat. **15**:73 (April) 1948.

A case of gangosa in a 7 year old boy is described. The disease first began to manifest itself when the boy was 4 years old. The author considers penicillin followed by plastic surgery the treatment of choice.

MCGUIGAN, Evanston, Ill.

LAMBLIASIS IN CHILDHOOD. S. BARBERI, Ann. ital. di pediatrie **1**:16 (Dec.) 1948.

The author, after a critical examination of the question of the pathogenic importance of Giardia lamblia, reports on 250 clinical cases of lambliasis observed in the last five years and on the remarkable diffusion of Giardia in the province of Messina and in Calabria.

The picture most frequently seen is that of enterocolitis dysenteriform; the course is sometimes acute, most frequently subacute or chronic. There are not infrequently cases of dyspepsia, accompanied sometimes in nurslings with dystrophy.

The author mentions some clinical pictures less frequently seen, and he illustrates some cases of Herter's disease (intestinal infantilism), toxicosis, hepatobiliary syndrome, pseudo-tuberculous syndrome, hypochromic anemia, dermatitis, pellagra syndrome and allergic syndrome. The therapy of choice is acridinic treatment supplemented in the chronic forms by arsenical treatment.

FROM THE AUTHOR'S SUMMARY.

SHOULD ONE DISCOURAGE BREAST FEEDING WHEN THE MOTHER HAS A BRUCELLAR INFECTION? G. LODI and R. OLIVO, Lattante **19**:461 (Aug.) 1948.

Four months after the birth of her baby a nursing mother contracted undulant fever and was ill for two months. Laboratory tests on the mother's blood confirmed the diagnosis. The mother continued to nurse her infant during the illness; the infant remained well and gained satisfactorily in weight. No organisms were found in the mother's milk on culture, and agglutination tests on the infant's serum gave negative results. The authors maintain that not all infants must be weaned when the mother contracts undulant fever; weaning is necessary only when the mother is very ill or when the milk supply becomes inadequate.

HIGGINS, Boston.

INFECTIOUS LYMPHOCYTOSIS. LUIS BARRERAS AREU, Rev. cubana de pediat. **19**:569 (Oct.) 1947.

The author presents two cases of acute infectious lymphocytosis in young children. In one case there were 85,500 leukocytes, of which 84 per cent were lymphocytes. In the other case the leukocyte count was 70,000, with 71 per cent lymphocytes. The cells appeared normal, and in one case the sternal marrow was normal. The heterophile antibody tests elicited negative reactions. The clinical course is benign, and the picture should not be confused with that of leukemia.

KEITH, Rochester, Minn.

MALARIA IN INFANTS. M. LOPEZ PONDAL, Rev. Soc. puericult. Buenos Aires **13**:54 (July-Sept.) 1947.

Malarial "primary infection" starts as an acute febrile episode lasting from one to three days. After this the intermittent rhythm becomes established.

At first the presumptive diagnosis is made by exclusion, since splenic enlargement is not frequent and, even so, it may be found in normal infants. Rarely the disease is afebrile, and the infant becomes dystrophic. Three rather infrequent forms of the disease are described: (1) abdominal, with fever and abdominal pain which may simulate appendicitis and even peritonitis; (2) edematous (the edema may be limited to the face or be generalized), and (3) nervous, with fever, convulsions and encephalitis.

BUNGE, Parkersburg, W. Va.

STAPHYLOCOCCUS SEPTICOPYEMIA WITH PURULENT PERICARDITIS. FERNANDO MARTINEZ L. DE G., Rev. chilena de pediat. **337**: (April) 1948.

The good results obtained in the treatment of a patient with suppurative pericarditis as a complication of Staphylococcus aureus septicemia are described. The patient, a boy of 10, recovered after treatment with penicillin, which was given intramuscularly and was also injected directly into the pericardial sac before and after a pericardiostomy was done. A follow-up examination of the boy three years after the operation showed no further cardiovascular complications and a very satisfactory general condition.

FROM THE AUTHOR'S SUMMARY.

PENICILLIN THERAPY IN GONORRHEA OF CHILDREN. ALFREDO WIEDERHOLD and ANTONIETA MENDEZ, Rev. chilena de pediat. **19**:352 (April) 1948.

The authors present a new series of cases of children with gonococcic infection who were treated with penicillin by oral administration.

FROM THE AUTHORS' SUMMARY.

FATAL TRICHINOSIS IN A BOY. SANTIAGO RUBIO, Rev. chilena de pediat. **21**:37 (Jan.) 1950.

The author reports a case of trichinosis complicated by a pneumonia in an 11 year old boy who died on the eighth day in the hospital.

FROM THE AUTHOR'S SUMMARY.

PENICILLIN TREATMENT OF THE SYNDROME OF REITER. KARL BLANKE, Med. Klin. **44**:1116 (Sept. 2) 1949.

The classic triad of symptoms for Reiter's disease, later called the syndrome of Reiter, is urethritis, keratoconjunctivitis and arthritis with fever. The causes differ. The case of a 10 year old girl in whom the disease yielded to an intensive treatment with penicillin started on the eighth day of the disease is reported. From the aspirated material of the diseased right knee joint a gram-positive coccus was isolated.

AMBERG, Rochester, Minn.

RHEUMATIC FEVER AND TONSILS. E. GYÖRGY, Paediat. danub. **5**:340 (June) 1949.

Tonsillectomy is indicated in all forms of rheumatic fever if the patient has repeatedly suffered from acute tonsillitis or if there is a chronic inflammation of the tonsils. However, in similar cases other infectious foci should be also eliminated. In case of focal infection the patient should not be operated on before acute symptoms have disappeared. Early tonsillectomy may involve complications in labile allergic states. The bacterial flora of the normal pharynx is fairly constant, and there are no relevant changes in the tonsils of children suffering from rheumatic disease. Prophylactic tonsillectomy does not significantly inhibit the involvement of joints. Similarly, tonsillectomy following an acute rheumatic infection has very little, if any, prophylactic effect on the frequency of relapses.

FROM THE AUTHOR'S SUMMARY.

TRICHOSTRONGYLUS INFESTATION AND EXTRAPYRAMIDAL LESION: EXOGENOUS WILSON'S DISEASE? P. V. VÉGHELYI, G. G. MAKARA and M. FLAMM, Paediat. danub. **4**:196 (Oct.) 1948.

A 7 year old girl who had had no complaints and had been developing well became infested with Trichostrongylus vitrinus. The source of infection was a goat. Three months after infestation talipes varus of nervous origin appeared. The worms were eradicated, and two months later the nervous complaints ceased. Three months later she became reinfested. In another four months the nervous complaints appeared in an increased degree. The parasites could again be removed, after which her condition improved. However, she soon became reinfested again, and this time the worms could not be expelled. The patient was again seen 10 years later and was suffering from a nervous condition characteristic of Wilson's disease. The question of whether the disorder of the central nervous system might be in pathogenetical connection with the toxic effect of trichostrongylus may arise. The case of the patient reported plus those of 26 other children who were found by the authors to harbor this parasite were the first cases of human infestation with Trichostrongylus observed in central Europe.

FROM THE AUTHORS' SUMMARY.

TWO RARE FORMS OF CHRONIC RHEUMATISM. JIŘÍ LUKES, Pediat. listy, 1949, no. 3, p. 107.

Two cases are described. In the first patient, a 9 year old girl, the disease had a course similar to Still's disease; in the second patient, a 13 year old girl, the disease was similar to the Felty syndrome.

FROM THE AUTHOR'S SUMMARY.

TENDENCY TOWARD BLEEDING IN THE COURSE OF ACUTE RHEUMATISM. JOSEF HOUSTEK and JIRI JANELE, Pediat. listy **4**:148, 1949.

Bleeding in acute rheumatism is rare, with the exception of epistaxis and terminal bleeding in decompensation (among 747 cases, there were 35 of epistaxis, 5 of hematuria, 4 of hematemesis, 4 of hemoptysis, 6 of petechial bleeding on the skin and mucous membranes and 3 of hemorrhagic exanthem). Cases of the Chester and Schwartz type were not observed. There were no cases of serious hypoprothrombinemia after administration of salicylates. In an analysis of 37 cases of anaphylactoid purpura, there was not a single case of anaphylactoid purpura occurring simultaneously with rheumatism nor even a transition between these two diseases.

FROM THE AUTHORS' SUMMARY.

CHRONIC MALARIA WITH HEPATOSPLENOMEGALIC SYNDROME. ALOIS BUCEK, Pediat. listy **4**: 153, 1949.

A case of untreated chronic malaria with hepatosplenomegaly in a 14 year old girl is described. Death occurred after splenectomy.

FROM THE AUTHOR'S SUMMARY.

A CASE OF HYDATID CYSTS IN THE SACRAL BONE. A. AFENTAKI and M. TSERBIS, Acta Soc. pediat. hellen. **2**:117 (May-June) 1948.

A 14 year old girl complaining of pains in the sacral region and along the distribution of the sciatic nerve was found on examination to have signs suggesting pressure on the sacral nerve roots. The cause was found at operation to be multiple hydatid cysts which had invaded the sacrum and after erosion of the anterior surface were pressing against the rectum.

DOXIADIS, Sheffield, England.

RICKETTSIALPOX. FREDERICK REISS, Chinese M. J. **67**:390 (July) 1949.

Since 1946, 477 cases of rickettsialpox, a new disease, have been recognized in New York City. The infection is acquired from mites parasitizing on mice. The disease starts with a small papular primary lesion that may occur anywhere on the body. Five to seven days later a remittent fever accompanied with a maculopapular or vesicular eruption develops. This eruption is sparse, may occur on any part of the body, produces no subjective symptoms referable to the skin and disappears in 30 to 48 hours. The fever may last seven to 10 days.

Diagnosis may be confirmed by a specific complement fixation test. Treatment is symptomatic. There have been no deaths.

MACDONALD, Pittsburgh.

Chronic Infectious Diseases

PROTECTIVE VACCINATION AGAINST TUBERCULOSIS WITH SPECIAL REFERENCE TO BCG VACCINATION. JOSEPH D. ARONSON, Am. Rev. Tuberc. **58**:255 (Sept.) 1948.

After a historical résumé of the various attempts to control the tuberculous process by vaccines, Aronson describes the development of BCG and the criteria by which its value may be determined. He bases his observations on the now well known study of the results of BCG vaccination of large groups of Indians living on reservations in various parts of the United States and Alaska. He describes in detail the measures used to determine its effectiveness in a population having a high morbidity and mortality rate and compares the results with data obtained from comparable controls living in the same environment.

In this study freshly prepared BCG vaccine was administered to 1,551 American Indians ranging in age from 1 to 20 years and to 123 newborn infants. The control group consisted of 1,457 Indians and 139 newborn infants. Both groups were followed over a period of from nine to 11 years by means of tuberculin tests and roentgenograms; the newborn infants were followed for six to eight years.

During this period, among the vaccinated subjects there occurred a total of 55 deaths, six from tuberculosis. Among the controls there were 109 deaths, 53 from tuberculosis. Among the vaccinated newborn infants, seven died, none from tuberculosis. Among the controls, 15 died; four from tuberculosis. Roentgenologically demonstrable lesions having the characteristics of primary tuberculosis occurred in 22 of the vaccinated and 120 of the unvaccinated subjects. Evidence of more advanced tuberculosis was found in 21 of the vaccinated subjects and 93 of the controls.

Accumulated data, both experimental and clinical, indicate that an initial infection with viable virulent or attenuated tubercle bacilli induces increased resistance to reinfection with virulent bacilli. There is, therefore, a sound basis for the use of the attenuated viable BCG strain of tubercle bacillus as an immunizing agent. There is room for difference of opinion as to the advisability of the universal use of the vaccine. Its use is indicated, however, in areas

where morbidity and mortality from tuberculosis are high and where facilities for care are inadequate. Its use is also indicated in the case of medical personnel and others who are tuberculin negative and who may be exposed frequently to tuberculous infection.

EUGENE SMITH, Ogden, Utah.

STREPTOMYCIN-PROMIZOLE THERAPY OF MILIARY AND MENINGEAL TUBERCULOSIS IN CHILDREN. EDITH M. LINCOLN and THOMAS W. KIRMSE, Am. Rev. Tuberc. **61**:159 (Feb.) 1950.

Streptomycin is the most effective tuberculostatic agent available, and preliminary reports of its use in treatment of miliary and meningeal tuberculosis were favorable More prolonged observation proved that the end results were not so good as had been anticipated. Prolonged use of this drug frequently produced damage to the vestibular branch of the eighth nerve and had a tendency to result in the development of resistant forms of the tubercle bacillus. These unfavorable reactions limited its use for patients with miliary and meningeal forms of tuberculosis, for whom long term administration of the drug is mandatory.

Since these unfavorable reactions imposed a limitation on the prolonged use of streptomycin, the authors developed a plan of treatment in which administration of streptomycin intramuscularly and intrathecally was continued for from 120 to 180 days and in addition thiazolsulfone (promizole®) was given orally for a period of three years. The dosages and method of administration are given in detail in this paper. The results of this treatment in 13 cases of miliary tuberculosis and 21 cases of tuberculous meningitis are encouraging. Eleven patients with miliary tuberculosis and 16 patients with tuberculous meningitis survived. Three patients with meningitis suffered a relapse; one of these died. In cases of tuberculous meningitis early recognition of the clinical picture and intensive intrathecal therapy are important. The location of the lesion, the sensitivity of the micro-organisms and possibly the age of the patient at the onset of the meningitis are important in prognosis.

Combined therapy with streptomycin and thiazolsulfone, properly administered, appears to have improved the results in the treatment of these diseases and is worthy of more extensive clinical trial.

EUGENE SMITH, Ogden, Utah.

CHEMOTHERAPY OF TUBERCULOSIS IN CHILDREN. EDITH M. LINCOLN and THOMAS W. KIRMSE, Pediatrics **5**:280 (Feb.) 1950.

Streptomycin is the most effective tuberculostatic agent, but it is unsuitable for prolonged therapy because of its potential toxicity and the tendency of the tubercle bacillus to become resistant to it.

Streptomycin is of great value in controlling tuberculosis so as to permit surgical procedures and allow collapsed lung therapy. It should not be used in treatment of uncomplicated primary tuberculosis and minimal chronic pulmonary tuberculosis because these forms of the disease usually respond to conservative management. It should not be used in an attempt to prevent complications; meningitis and less serious complications may develop during treatment.

Seven patients with acute generalized miliary tuberculosis were treated with a sulfone, thiazolsulfone (promizole®). Five of them are living 2½ to five years after treatment was started. The pulmonary miliary mottlings cleared completely in an average of eight months. There were no cases of relapse, and in none of the patients did meningitis develop.

Combined therapy with streptomycin and thiazolsulfone was undertaken in order to utilize the advantages of the rapid action of the antibiotic with the prolonged bacteriostatic action of the sulfone. Thiazolsulfone can be given safely and effectively for years.

In the treatment of miliary tuberculosis by combined therapy, 1.0 Gm. streptomycin (0.5 Gm., twice daily) is given intramuscularly for 120 days, and 1.0 to 8.0 Gm. thiazolsulfone (0.25 to 2.0 Gm., four times daily) is given orally for three years. The initial dose of 1.0 Gm. daily is given for several days. In the absence of signs of toxicity, a gradual steplike increase from 1.0 to 2.0 Gm., or higher, is then made every few days or weekly until therapeutic blood thiazolsulfone levels (taken three hours after the last oral dose) between 1.0 and 3.0 mg. per 100 cc. are obtained. Ten patients with miliary tuberculosis were treated by combined therapy.

Eight remain well six to 23 months after treatment was started. The pulmonary miliary mottlings cleared in an average of nine weeks. No relapse of miliary tuberculosis occurred, but survivors in whom meningitis developed have made good recoveries.

In the treatment of tuberculous meningitis by combined therapy, 1.0 Gm. streptomycin is given intramuscularly for 180 days. In addition, 0.1 Gm. is given intrathecally once daily until toxic symptoms occur. Thereafter, this amount is given every two days, but if toxic symptoms again occur, 0.05 Gm. is given every two or three days until a series of 40 injections has been completed. Thiazolsulfone is administered by the same method prescribed for miliary tuberculosis. Eighteen patients with tuberculous meningitis have been treated by this method. Thirteen patients survive five to 23 months after therapy was begun. All the survivors are apparently normal mentally.

FROM THE AUTHORS' SUMMARY.

NATURAL HISTORY AND PATHOGENESIS OF MILIARY AND MENINGEAL TUBERCULOSIS IN CHILDREN: ANALYSIS OF 163 CASES. THOMAS L. PERRY, Pediatrics **5**:988 (June) 1950.

In preparation for a program of treatment of miliary and meningeal tuberculosis with streptomycin and other antituberculosis drugs, the cases of 163 consecutive admissions to the Los Angeles Childrens Hospital in the 15 years between 1933 and 1948 were analyzed. Twenty-one infants and children had miliary tuberculosis, 58 had tuberculous meningitis and 84 had both diseases. Of 145 patients who received only symptomatic treatment, all died. The usual frequency of these diseases in the spring was not observed in this series. Allergy to tuberculin was uncommon; only 2 per cent of the patients reacted negatively to 1.0 mg. old tuberculin.

Forty-eight per cent of the cases occurred before the age of 2 years and two thirds of them before the age of 4 years. There was pathologic evidence that tuberculous meningitis occurs commonly within a few months of the primary infection; in 82 per cent of the cases in which autopsy was done there was evidence of fresh primary tuberculosis.

Vague symptoms such as vomiting, fever and lethargy were most frequent in early tuberculous meningitis and rarely stimulated a prompt diagnosis. Headache was a frequent complaint in children over 4 years of age but was uncommon in those under 4 years. The average duration of life of patients with tuberculous meningitis from onset of symptoms to death was 20 days; the duration of symptoms until a correct diagnosis was made averaged over 11 days.

Caseous tuberculosis foci antedating the meningitis were demonstrated in the central nervous system in 27 of 70 cases in which careful pathologic examination was made. In 35 per cent of the cases of tuberculous meningitis in which autopsy was done there was no acute hematogenous dissemination elsewhere in the body. Hydrocephalus was found in 25 of 70 brains examined and tended to appear early in the course of the disease. Possible precipitating factors were found in the histories of 15 per cent of the 163 patients.

Suggestions are made as to possible means of preventing the development of miliary and meningeal tuberculosis in infants and children, and the need for prompt diagnosis and treatment is stressed.

FROM THE AUTHOR'S SUMMARY.

SERUM AGGLUTININS AND TUBERCULIN TESTS FOLLOWING BCG VACCINATION. R. SOHIER, Presse méd. **56**:470 (July 3) 1949.

Sohier used the serodiagnostic test of Arloing and Courmont to measure the specific agglutinins produced by BCG vaccination. In subjects who had no demonstrable agglutinins before vaccination, agglutinins appeared after vaccination. In subjects already possessing agglutinins, a higher value was found in 56 per cent, a similar value in 44 per cent, after vaccination.

Skin tests with tuberculin showed results dissociated from the agglutinin values. If a subject had no agglutinins previous to vaccination, his tuberculin reaction remained negative, although specific agglutinins developed. If the subject already had agglutinins, or if he was given a second vaccination, his skin reaction became positive, while the agglutinin value usually increased.

These facts should be of interest in the study of the indications for revaccination with BCG.

DAFFINEE, Melrose, Mass.

THE COURSE OF THE SEDIMENTATION RATE IN UNCOMPLICATED CASES OF PRIMARY TUBERCULOUS INFECTION WITH ERYTHEMA NODOSUM IN CHILDREN. KURT HOLMDAHL, Ann. pædiat. **173**:222 (Oct.) 1949.

The original material for this study consisted of 142 cases of uncomplicated primary tuberculous infection with erythema nodosum. Satisfactory data on the behavior of the sedimentation rate were obtained in 131 cases. The patients were followed over a period averaging 10 years. Data from all patients with postprimary tuberculosis were discarded. The difficulty of obtaining reliable information as to whether any nonspecific infection contributed to the rise in the sedimentation rate is pointed out. Rises due to this cause were, to the furthest possible extent, excluded from consideration.

The following figures on the duration of the elevated sedimentation rate obtained: A duration of two months was found in 51 of 131 cases (38.9 per cent); a duration of six months was found in 102 cases (77.9 per cent). In seven cases the duration exceeded 18 months. No difference in the duration between the age groups 0 to 9 and 9 to 15 years was definitely demonstrable. The especially protracted cases, however, were more numerous in the younger age group.

The sedimentation rate curve had in about one half of the cases a smoothly falling course without renewed rises. In the rest of the cases there appeared one or more rises. A curve found in approximately every third case of the present analysis is pointed out. It consists of an initial rapid drop to normal values, with a renewed sedimentation rate rise immediately thereafter, this continuing for a long or short period.

There is often a discrepancy between the course of the sedimentation rate curve and the roentgenologic tuberculous changes. In regard to these cases, the possibility of a hematogenous or lymphogenous spread from the primary focus is discussed.

FROM THE AUTHOR'S SUMMARY.

INVESTIGATIONS OF BCG TUBERCULIN. J. HENNING MAGNUSSON, ARNE LITHANDER and ERIK HABGERG, Ann. pædiat. **173**:253 (Oct.) 1949.

There seems to be a consensus that tuberculin sensitivity such as arises as a reaction to living tubercle bacilli signifies a specific immunity against tuberculosis. If this is so, then the results of the comparison between BCG tuberculin and standard tuberculin shown by the authors should be considered as proof that in many cases a specific immunity exists with use of the Calmette inoculation before a positive tuberculin reaction is obtained with 1 mg. of standard tuberculin. The time from the day when a positive BCG tuberculin reaction is found until the tuberculin reaction is also positive to standard tuberculin can be long and may be as long as several weeks. This is the case particularly with children who had been inoculated during their first few days of life and in whom we can expect protection from the inoculation a considerable time before the tuberculin reaction to standard tuberculin could be positive.

FROM THE AUTHORS' SUMMARY.

INVESTIGATIONS OF THE PATHOGENESIS OF TUBERCULOUS TOXIC-ALLERGIC MENINGEAL REACTION IN CHILDREN. D. MÓRITZ, Helvet. paediat. acta **2**:332 (Aug.) 1947.

Móritz reports seven cases of meningitis tuberculosa toxicoallergica in babies with primary tuberculosis and premature dissemination. An examination of the fluid showed an increased pressure, clear fluid, positive Pandy reaction, slight increase in number of cells and protein values and no tubercle bacilli. At autopsy a primary infection of the lungs and, with one exception, premature dissemination were found in all the patients. Study of sections of the brain showed tuberculoma in five patients, while in two tuberculous foci were not found in the brain substance and in the meninges, but only edema and hyperemia.

FROM THE AUTHOR'S SUMMARY.

TOXOPLASMOSIS AS A CAUSE OF CONGENITAL DEFECTS. H. M. DEKKING, Ophthalmologica **117**:1 (Jan.) 1949.

Toxoplasmosis is a more frequent cause of congenital defects than is usually assumed. It was found to produce the following defects: (1) congenital falciform detachment of the retina; (2) microphthalmos; (3) congenital cataract; (4) "coloboma" of the macula, which on histo-

logic section was found to be central choroiditis, and (5) "pseudoglioma," which on section proved to be congenital total detachment of the retina. The author describes two cases in detail and bases his conclusions on a large number of cases he has seen. He stresses the point that any child showing one or several of the aforementioned signs should be examined for toxoplasmosis by means of roentgenograms, roentgenography of the skull, determination of spinal fluid pressure, tests for xanthochromia of the spinal fluid and a serum neutralization test.

H. P. KIRBER [ARCH. OPHTH.].

SERIAL ROENTGENOGRAPHIC EXAMINATIONS IN CHILDHOOD: EXPERIENCE AND RESULTS. R. GARSCHE, Schweiz. med. Wchnschr. **79**:39 (Jan. 15) 1949.

In regard to serial roentgenologic examinations of the lungs, with reference to tuberculosis, the conclusion is reached that children under 6 years of age should be excluded from such serial examinations. Children up to the ninth year do not permit undisturbed examinations and considerable time and waste of material are needed in order to arrive at satisfactory results. For children over 10 years, the examination is satisfactory, although the process is somewhat slower than with adults. It requires a specially trained personnel to conduct such serial examinations in children. The interpretation should be done by a commission consisting of the chief of the roentgenology department, a pediatrician trained in roentgenology and a health department physician. With regard to the diagnosis of tuberculosis, general mass examinations are entirely too expensive. Only when special indications exist should such examinations be conducted.

AMBERG, Rochester, Minn.

A NOVEL METHOD OF KEEPING TUBERCULIN P.P.D. (PURIFIED PROTEIN DERIVATIVE). PAUL HAUDUROY, Schweiz. med. Wchnschr. **79**:999 (Oct. 22) 1949.

Lyophilized solutions of purified protein derivative of various concentrations are kept in specially designed ampules. It is possible by adding 1 ml. of solvent to obtain solutions of various strengths for the Mantoux test, being assured of a uniform unchangeable preparation.

AMBERG, Rochester, Minn.

OCCURRENCE OF EPIDEMIC MENINGITIS IN CHILDREN WITH MENINGITIS TUBERCULOSA. K. B. CHOREMIS, N. ZERVOS, B. KONSTANDINIDIS, S. PANTAZIS and G. BELISSAROPOULOS, Schweiz. med. Wchnschr. **80**:138 (Feb. 11) 1950.

That tuberculous meningitis may become complicated with meningococcic meningitis has been reported. The authors have observed six such cases, in five of which the patients were less than 3 years old. These patients had been treated with streptomycin. Four of these cases are reported in more detail, with autopsy findings. These patients suddenly become much worse with the onset of the meningococcic meningitis.

AMBERG, Rochester, Minn.

THE EFFECTS OF MEASLES ON TUBERCULOUS MENINGITIS UNDER TREATMENT BY STREPTOMYCIN. G. SALVIOLI and L. MARTONI, Clin. pediat. **29**:449 (Aug.) 1947.

Measles developed in three children while they were under treatment with streptomycin for tuberculous meningitis. Examination of the spinal fluid after the children had recovered from the febrile phase of the measles revealed fewer cells in each case, diminished protein in one case and increased sugar in two cases. In each case there was clinical improvement.

These findings may be significant (1) because measles lowers the sensitivity of the patient to tuberculin and (2) because measles usually aggravates a tuberculous infection.

HIGGINS, Boston.

THE PASSAGE OF PARAAMINOSALICYLIC ACID INTO THE SPINAL FLUID IN TUBERCULOUS MENINGITIS. L. MARTONI and P. NICOLAJ, Clin. pediat. **31**:1 (Jan.) 1949.

Observations were made on 15 patients who were ill with or had recovered from tuberculous meningitis. Paraaminosalicylic acid, 2.5 Gm., was given by mouth. One hour later specimens of blood and spinal fluid were withdrawn and analyzed for paraaminosalicylic acid. When

there was no inflammation of the meninges, no paraaminosalicylic acid was found in the spinal fluid. When meningeal inflammation was present—as indicated by an increased cell count and a positive reaction to the Pandy test—paraaminosalicylic acid was found in the spinal fluid in a concentration of from 10.6 to 33.7 per cent of that in the blood; the degree of inflammation was not necessarily proportional to the concentration of paraaminosalicylic acid in the spinal fluid. The concentration of paraaminosalicylic acid in the blood varied from 800 to 2,900 micrograms per 100 cc.

A bibliography and a good summary of the literature on the therapeutic use of paraaminosalicylic acid are given.

HIGGINS, Boston.

ANATOMICAL AND PATHOLOGICAL CONSIDERATIONS REGARDING CASES OF TUBERCULOUS LEPTOMENINGITIS TREATED WITH STREPTOMYCIN. V. ACCORDI and F. DOTTI, Lattante **19**:449 (Aug.) 1948.

Autopsy reports are given for five children who had had tuberculous meningitis and had lived two to six months after the beginning of streptomycin therapy. The anatomic and histological pictures showed striking and individual differences for each patient, although hydrocephalus was a constant observation. The nature and treatment of this concomitant hydrocephalus are not as yet well established.

HIGGINS, Boston.

THE DERMOCHROMOGRAPH, USING THE PHOTOELECTRIC CELL, IN THE EVALUATION OF INTRADERMAL TUBERCULIN REACTIONS. E. EGIDI and RAFFAELLA DIENA, Minerva pediat. **1**:51 (Feb.) 1949.

The photoelectric cell was used to determine the absorption of light in the area of a tuberculin reaction. The findings on successive days are plotted and made use of in evaluation of the intensity of the reaction.

HIGGINS, Boston.

CHEDIAK TEST IN INFANTS. J. E. VIRASORO, J. C. PELLERANO and J. SABON SALABERRY, Rev. Soc. puericult. Buenos Aires **13**:25 (Jan.-June) 1947.

Congenital syphilis is characterized by the absence of outstanding symptoms. The Chediak test is simple and easy to read, and the material is easily obtainable in a well baby station. The results of this test run parallel with the results of classic serologic tests, and, according to Barzizza, the proportion of nonspecific positive reactions is very low.

During a four year period more than 1,000 Chediak tests were performed on patients of a well baby station. Figures for infants under 2 months of age were excluded from the statistics. The results obtained confirm the importance of the enlargement of the spleen and liver in the discovery of congenital syphilis in infants.

Of the whole series, 2.58 per cent gave positive reactions to the Chediak test. Among infants with hepatomegaly, 8.70 per cent were found to have positive reactions. Among those with barely palpable spleen, 13.24 per cent showed positive reactions. Among those with splenomegaly, 28 per cent and among those with enlarged liver and spleen, 30.16 per cent showed positive reactions.

Chediak's method is recommended for the use of rural physicians who cannot depend on adequate laboratory facilities.

BUNGE, Parkersburg, W. Va.

EXTRAPULMONARY PRIMARY TUBERCULOUS INFECTION. FERNANDO MARTINEZ, Rev. chilena de pediat. **19**:500 (June) 1948.

Two cases of primary extrathoracic tuberculous infection are reported. The ports of entry of the infection were one, in the skin of the forehead; the other, on the left cheek, following dental treatment. Both patients presented submaxillary adenopathy; a smear revealed tubercle bacilli in the second case. In each case the lack of pulmonary lesions (fluoroscopy and chest films), the result of the tuberculin test and the clinical course permitted the diagnosis.

The first patient's mother showed a tuberculous cavern in the right lung and tubercle bacilli in the sputum.

FROM THE AUTHOR'S SUMMARY.

CONGENITAL SYPHILIS IN TWINS. H. LAUSECKER, Wien. klin. Wchnschr. **62**:85 (Feb. 3) 1950.

Nonidentical twins with congenital syphilis were affected in different degrees. The boy had a syphilitic coryza at the age of 4 months; at the age of 6 months he died with pneumonia in spite of penicillin therapy. Besides the coryza, a periostitis of all long bones and a gumma of the right upper mandible were found. At postmortem examination spirochetes could not be found. The other twin, a 7 month old girl, had no clinical signs of syphilis. A slight periosteal thickening of the diaphyses of the humeri was noted, and the Wassermann reactions of the cerebrospinal fluid were negative, but the "luotest" elicited a positive reaction. The infant was treated, and on reexamination after six months, only the "luotest" reaction remained positive. The mother, a primipara, had no clinical signs of syphilis and was never treated. The blood serum and the cerebrospinal fluid Wassermann reactions were positive. The father's blood serum Wassermann reaction was repeatedly negative. The literature is discussed. Perhaps the most interesting feature is that in cases of nonidentical as well as of identical twins it has been reported that one of the twins did not have the disease.

AMBERG, Rochester, Minn.

OBSERVATIONS ON TREATMENT OF TUBERCULOUS MENINGITIS WITH STREPTOMYCIN. R. DUBOIS, R. LINZ, H. LESCHANOWSKI, R. SCHLESSER and R. WATTIEZ, Acta pædiat. belg. **1**:195, 1946-1947.

This rather complete work on the present day knowledge concerning streptomycin treatment of tuberculous meningitis originated from the University of Brussels and covers an entire issue of the *Acta pædiatrica belgica*. The information is derived from the literature and from study of over 80 patients, some of them observed over a year's period. The patients are divided into five groups. The first group, consisting of 12 patients with tuberculous meningitis without miliary tuberculosis, were observed over a period of from 10 to 12 months and were treated intraspinally and intramuscularly. After the experiences with the first group, the authors standardized their method of management and treated 13 patients, these comprising the second group, by the mixed treatment of daily intrathecal and intramuscular injections for 45 days, followed by a rest period of 20 days and then another treatment period, of 20 days. The dosage was 40 to 50 mg. per Kg. a day intramuscularly and 50 to 100 mg. intrathecally. The third group was treated by intraspinal injection only. The fourth and fifth groups were given smaller and less frequent doses.

The diagnostic criteria used were: history; physical findings; roentgenograms of the chest; tuberculin skin test; results of chemical, microscopic and bacteriologic examination of the spinal fluid, culture, and guinea pig inoculation. The search for Mycobacterium tuberculosis on the slide did not give satisfactory results; and culture and animal inoculation, although essential for the critical evaluation of such a study, were of no help in the diagnosis because of the length of time needed before reports could be obtained. From a prognostic point of view Dubois and associates felt that the occurrence of hydrocephalus was an unfavorable sign. Of six patients with miliary tuberculosis, one was admitted when the disease was in a terminal stage and the five others survived; the roentgenograms of these showed complete healing.

The authors draw the following conclusions: The previously rapid aggravation and fatal outcome of tuberculous meningitis can be markedly altered by their method of intramuscular and intrathecal streptomycin injection. The progress of the disease during the first five months is decisive for the final outcome; after this time convalescence occurs. The prognosis of these first five months with regard to life as well as with regard to neurological sequelae depends on the early start of treatment. Relapses after a five month observation period are considered as possible. Miliary tuberculosis is equally benefited by this type of treatment. Of 26 patients observed, 21 survived the fifth month of the disease and of these 19 left the hosiptal.

The authors are continuing their observations on this series of patients.

GLASER, Chicago.

MILIARY AND MENINGEAL TUBERCULOSIS TREATED WITH STREPTOMYCIN. R. FONÓ, Orvosok Lapja **4**:769 (June 13) 1948.

Fonó reports on the use of streptomycin treatment for eight patients with meningeal tuberculosis and four patients with miliary tuberculosis. Three of the eight patients treated for meningeal tuberculosis are alive; two of them have recovered, the third being still under treatment. One of the four patients with miliary tuberculosis can be considered as having recovered. Three are still under treatment and show considerable improvement. Without doubt, streptomycin is effective in the treatment of these two most serious tuberculous diseases. It changes the process of meningitis into a chronic, slowly progressing process, showing sometimes symptoms of encephalitis.

GÖRGÉNYI-GÖTTCHE, Budapest, Hungary.

TUBERCULOUS NODOSE PANARTERITIS. I. FLESCH, Paediat. danub. **2**:224 (Oct.) 1947.

A tuberculous child of 2½ years of age was observed. He had a diffuse nodose exanthem that differed from typical erythema nodosum both clinically and histologically. The condition began with high fever and a great number of pale eruptions on all the surfaces of the limbs. A small, hard, pellet-like nodule could be palpated deep under the surface of each patch. There was neither itching nor pain. A lytic fall in temperature occurred, and the eruption disappeared within a week leaving no traces.

The histologic specimen was characterized by endarteritis, mesarteritis, periarteritis and thromboses of the arteries in the subcutis, with perivascular infiltrations. No bleeding or necrosis was seen. No pathologic organism could be detected. There were no means for making cultures or animal experiments to prove the presence of tubercle bacilli.

The tuberculous origin of the process could be taken for granted on the basis of the clinical appearance of the condition and its further development, as after a time mediastinal pleurisy appeared. It is probable that some allergic reaction brought about the changes observed.

The condition must be differentiated from typical erythema nodosum and should be called tuberculous nodose panarteritis.

FROM THE AUTHOR'S SUMMARY.

THE EFFECT OF BENADRYL ON TUBERCULIN SENSITIVITY. C. THOMOPOULOS, Acta Soc. pediat. hellen. **2**:49 (March-April) 1948.

Fourteen infants and children with positive reactions to old tuberculin (Mantoux) were given intradermal injections of 0.01 mg. of old tuberculin with 1 mg. or 0.01 mg. of diphenhydramine (benadryl®) hydrochloride. Injections of the same strength of old tuberculin and of the same amounts of diphenhydramine were used as controls.

It was observed (1) that diphenhydramine alone did not cause a tuberculin-type reaction when injected intradermally and (2) that the addition of 0.01 mg. of diphenhydramine to the solution of tuberculin increased the intensity of the reaction, whereas the addition of a hundred times stronger dose of diphenhydramine (i. e., 1 mg.) had the opposite effect.

DOXIADIS, Sheffield, England.

TUBERCULOUS CAVITY IN A FIVE MONTHS OLD INFANT. D. BEZOS and A. PANAGIOTAKI, Acta Soc. pediat. hellen. **2**:113 (May-June) 1948.

The authors report the case of a 5 month old infant with a tuberculous cavity in the upper lobe of the right lung. After 40 days of treatment with 0.24 Gm. of streptomycin daily, the roentgenologic examination, including tomography, showed a decrease in the size of the cavity.

DOXIADIS, Sheffield, England.

LIPODYSTROPHY OCCURRING IN A CASE OF TUBERCULOUS MENINGITIS. S. P. CHAROCOPOS and E. INGLESSI, Acta Soc. pediat. hellen. **2**:189 (Sept.-Oct.) 1948.

A 6 year old girl suffering from tuberculous meningitis was treated with intramuscular and intrathecal injections of streptomycin, and she was clinically improving. Two months after the onset of the illness and 50 days after the start of the treatment she complained of vertigo,

and tremor of the hands was noticed at the same time. Shortly afterward she started passing excessive amounts of urine, and her weight increased rapidly. A special type of obesity became apparent with accumulation of fat on the trunk while the extremities were spared. From careful clinical observations and laboratory investigations, the authors suspect that these symptoms and signs were manifestations of a lesion affecting the diencephalohypophysial system. It is not certain if the lesion is a result of the tuberculous meningitis or a toxic effect of the streptomycin.

DOXIADIS, Sheffield, England.

TUBERCULOSIS OF THE CHEST WALL. CHIA-SSU HUANG and MEI-SHIN STONE, Chinese M. J. **66**:125 (March) 1948.

Eight patients, four of whom were children, had either a cold abscess or a tuberculous sinus of the anterior chest wall. Radical excision of all visible tuberculous tissue resulted in cure in four cases, with complete healing of superficial tissue; in improvement in two cases, with small granulating wounds remaining, and failure in two cases. In the two cases in which failure occurred, exposed cartilages had not been excised completely.

MACDONALD, Pittsburgh.

TOXOPLASMOSIS. C. D. BINKHORST, Maandschr. v. Kindergeneesk **15**:1 (Jan.) 1947.

Encephalitis, chorioretinitis and intracerebral calcification are characteristic symptoms of infantile toxoplasmosis. Binkhorst describes a case of toxoplasmosis in which microphthalmia and psychomotor disturbances were also present. Toxoplasma-like bodies were demonstrated in the cerebrospinal fluid. This case of chronic disease is one of the few cases of nonfatal infantile toxoplasmosis diagnosed during life. Three other cases are described in which the possibility of toxoplasmosis should be considered.

VAN CREVELD, Amsterdam, Netherlands.

Diseases of Blood, Heart and Blood Vessels and Spleen

ROLE OF SPLENECTOMY IN THROMBOPENIC PURPURA. GEORGE BOGARDUS, J. GARROTT ALLEN, LEON O. JACOBSON and CHARLES L. SPURR, Arch. Surg. **58**:16 (Jan.) 1949.

After commenting on the variable results of splenectomy in cases of idiopathic thrombopenic purpura, the authors discuss the relation between the thrombocyte (platelet) count and the bleeding tendency. The importance of the capillary abnormality, as well as the low thrombocyte count, is emphasized. It is pointed out that the condition of the entire reticuloendothelial system and not of the spleen alone determines the course of the disease.

Clinical data based on 20 cases of idiopathic thrombopenic purpura are presented. Ten of the patients in this group were treated medically, and 10 were subjected to splenectomy. Seven of the 10 patients treated medically were known to have had no recurrence for a period of six months to two years. Five of the 10 splenectomized patients had a recurrence; in two of these patients the recurrence was severe. There was one death in the group which had undergone operation.

KAISER, Rochester, N. Y.

RECENT ADVANCES IN THE SURGICAL TREATMENT OF CONGENITAL LESIONS OF THE HEART AND GREAT VESSELS. W. E. ADAMS, Illinois M. J. **95**:40 (Jan.) 1949.

Effective surgical therapy for congenital lesions of the heart and great vessels has been the most recent development in thoracic surgery. This progress has been due chiefly to the clinical application of principles established through animal experimentation. Patients with a patent ductus arteriosis, tetralogy of Fallot or coarctation of the aorta may now have these lesions corrected and look forward to a more nearly normal life expectancy. With continued cooperative investigation, further development in this field may be expected.

FROM THE AUTHOR'S SUMMARY.

AN UNUSUAL CASE OF HEMORRHAGIC DISEASE IN AN INFANT. GRANVILLE H. NICKERSON, J. Pediat. **36**:96 (Jan.) 1950.

Nickerson describes a male infant with numerous ecchymotic areas over his body and a tendency toward severe and prolonged bleeding after minor trauma. He exhibited a prolonged bleeding time and a normal thrombocyte (platelet) count. The coagulation time was normal on several occasions and elevated on others. There was no family history of hemophilia. The author suggests that this is a case of atypical hemophilia.

MACDONALD, Pittsburgh.

LONG BONE INVOLVEMENT IN SICKLE CELL ANEMIA. JOHN R. ALMKLOV, ARILD E. HANSEN and MARTIN SCHNEIDER, Pediatrics **5**:204 (Feb.) 1950.

Two types of pathological changes may occur in the long bones of patients with sickle cell anemia. A hyperplastic bone marrow represents the response to continued destruction of erythrocytes, and this produces a wide medullary cavity and a thin cortex. The thromboses of vessels in the marrow and bone result in abnormal areas of calcification and new bone formation, producing a thick cortex and a small medullary cavity. The findings on roentgenographic examination will depend on which of the two processes is dominant.

A 21 month old Negro infant, whose symptoms of sickle cell anemia began at 4 months of age, showed typical roentgenographic findings resulting from a hyperplastic marrow. The cortex in the femur had become so thin that a pathological fracture resulted. This is the first reported instance of the occurrence of a pathologic fracture in sickle cell anemia.

FROM THE AUTHORS' SUMMARY.

STUDY OF CARDIAC ENLARGEMENT IN INFANCY WITH CASE REPORTS OF REVERSIBLE ENLARGEMENT. HYMAN GREEN and JOHN APLEY, Pediatrics **5**: 249 (Feb.) 1950.

Three cases are described in which cardiac enlargement in infants receded over a considerable period. In two of these cases cardiac hypertrophy appeared to originate in association with pulmonary infection. Some other possible causes of reversible cardiac enlargement are discussed.

To determine the incidence of all forms of cardiac enlargement, including reversible enlargement, 1,000 infants were examined roentgenologically in the neonatal period. In 16 infants considerable cardiac enlargement was present. Of these, seven died shortly; among the nine survivors, two were lost sight of, five had a congenital malformation of the heart and two recovered with an apparently normal heart.

To investigate the etiology of neonatal cardiac enlargement, the material from 200 consecutive autopsies was reviewed. In 29 cases considerable hypertrophy of the heart was found; in 8 of these a congenital malformation of the heart was present; 6 were cases of erythroblastosis fetalis, and in 5 some miscellaneous cause produced the cardiac enlargement. In the remaining 10 cases some pathological condition of the lungs was present.

It is suggested that some cases of cardiac hypertrophy are associated with pathological lung conditions occurring before, during or after birth. The association is not necessarily fatal, and the cardiac enlargement may prove reversible.

FROM THE AUTHORS' SUMMARY.

RIGHT HEART CATHETERIZATION OF THE AORTA THROUGH A PATENT DUCTUS ARTERIOSUS: REPORT OF TWO CASES. FORREST H. ADAMS, JOHN LABREE and HERBERT M. STAUFFER, Pediatrics **5**:390 (March) 1950.

The case reports of two patients with atypical findings of a patent ductus arteriosus are presented. Catheterization of the right side of the heart proved the existence of the condition by the passing of the catheter through the ductus into the aorta.

Catheterization of the right side of the heart in one of these patients demonstrated a right descending aorta in the presence of a left aortic arch. This was the fourth patient with this anomaly to be reported.

FROM THE AUTHORS' SUMMARY.

ELECTROCARDIOGRAM IN 679 HEALTHY INFANTS AND CHILDREN. MARGARET MARONEY and LOWELL A. RANTZ, Pediatrics **5**:396 (March) 1950.

One electrocardiogram was taken on each of 683 apparently healthy children under 9 years of age. Four of these who had a P-R interval of 0.16 second or more were shown to have cardiac abnormalities, and data from them were excluded from the study, leaving a total of 679 cases. The 679 electrocardiograms were analyzed, and the frequency of various findings at each year of age is presented.

T and P waves were frequently flat, diphasic or inverted in lead III. These changes were never observed in lead I and rarely in lead II.

The axis deviation on the standard limb leads was less than 0 degrees in three cases and greater than 90 degrees in three cases. No cardiac abnormality was demonstrated in these six children. Extreme right axis deviation (+ 130 degrees) is normal for children up to 6 months of age. The axis moves to the left with increasing age with the result that the average for 1 to 5 years inclusive is + 52 degrees. One of these six children, who did not return for further study, was 8 months old and showed a right axis deviation of + 100 degrees on the standard limb leads. It is probable that an axis deviation of + 100 degrees in this child was not an indication of cardiac disease. The axis deviation in each of the remaining five cases was probably adequately explained by the electrocardiographic position of the heart as demonstrated by unipolar limb and precordial leads.

The frequency distribution of QRS values followed a normal curve. The interval tended to increase slightly with increasing age from 6 months to 9 years. Intervals less than 0.04 second or greater than 0.08 second occurred in only four cases.

The frequency distribution of P-R (PQ) values followed a normal curve for from 2 to 8 years. The curve was skewed to the left in the 1 and 2 year groups because the conduction time rarely is less than 0.10 second. The measurement tended to increase with advancing age from 6 months to 9 years. Conduction times exceeding 0.15 second rarely occurred in healthy chlidren under the age of 9 years.

Both the P-R interval and the QRS interval tended to be longer with increase in height and weight. It was impossible to divorce these changes from those associated with age, since body size becomes greater as the child grows older.

No case was found with all of the diagnostic criteria of a Wolff-Parkinson-White syndrome.

The 23 children with P-R intervals of 0.16 second or more were studied extensively. Four were found to have definite cardiac abnormalities, and data on them excluded from the main study. The 19 remaining cases were included in the total, as no positive diagnosis of cardiac disease could be made. Some of these children may have been abnormal; data on them are presented in some detail for evaluation, and the final clinical impression is recorded.

It is of interest that of 23 apparently healthy children studied because of our finding (a conduction time exceeding 0.15 second), only 2 were perfectly normal so far as could be ascertained and only 3 had minimal evidence of an active infectious process of a type unknown, while in 7 there was good evidence and in 5 there was definite evidence of an active infectious process, possibly rheumatic fever. Probable rheumatic fever was the clinical impression in two cases, and cardiac abnormality was diagnosed in four cases.

Only data from the four patients with a definite diagnosis of cardiac abnormality were excluded from the frequency tables. Since some of the remaining 19 patients with conduction times greater than 0.15 second may not have been healthy, it is apparent that the occurrence of a P-R interval of 0.16 second or more is rare in a perfectly well chilld.

FROM THE AUTHORS' SUMMARY.

NONLIPOID RETICULOENDOTHELIOSIS (LETTERER-SIWE'S DISEASE). EDWARD HAVARD, LELLAND J. RATHER and HAROLD K. FABER, Pediatrics **5**:474 (March) 1950.

A case is presented of nonlipid reticuloendotheliosis (Letterer-Siwe disease) in a 15 month old girl showing the classic features of hepatosplenomegaly, anemia, leukopenia, thrombocytopenia, hemorrhagic diathesis, generalized lymphadenopathy, fever and a seborrhea-like dermatitis of the scalp. Unusual findings were the severe leukopenia and thrombocytopenia and the

presence of marked edema and ascites associated with hypoproteinemia. The relation to essential xanthomatosis (Hand-Schüller-Christian disease) and to eosinophilic granuloma is discussed.

FROM THE AUTHORS' SUMMARY.

ELECTRIC SYSTOLE (QT INTERVAL) IN ACUTE RHEUMATIC PERICARDITIS IN CHILDREN. LEO M. TARAN and DOTTY ORDORICIO, Pediatrics **5**:947 (June) 1950.

Thirteen cases of active rheumatic pericarditis in children are presented, and the diagnostic pattern and laboratory criteria are discussed. In addition to the usual electrocardiographic criteria of pericarditis, it is observed that the electric systole (Q-T interval) is shortened in all cases presented, irrespective of the type and severity of the attack.

A shortening of the duration of the Q-T interval during the course of active rheumatic carditis, in the absence of other factors (digitalis or salicylate therapy, hypopotassemia, hypocalcemia known to shorten the duration of the Q-T interval) should always suggest the presence of an acute pericarditis.

Incidence of normal duration of the Q-T interval in active rheumatic heart disease should be evaluated from this standpoint. The finding of a normal Q-T interval in a case of active rheumatic heart disease should not contraindicate the presence of active carditis but should indicate that the pericarditis has shortened the Q-T interval.

FROM THE AUTHORS' SUMMARY.

ANGIOCARDIOGRAPHY: ITS APPLICATION TO THE DIAGNOSIS OF COARCTATION OF THE AORTA. BERNARD S. EPSTEIN, Radiology **54**:211 (Feb.) 1950.

Epstein reports the angiocardiographic observations made on a 42 year old housewife, a 13 year old boy and a 14 year old girl. Iodopyracet injection U. S. P. (diodrast®) was seen in the descending aorta in all three patients. A notch on the aorta and dilated collateral circulation were the main diagnostic signs seen. The common diagnostic criteria, consisting of dilatation of the ascending aorta, enlargement of the left ventricle and inconspicuous or absent aortic knob, aided in the diagnosis. The author supports the conclusion that increased flow of blood through the intercostal arteries rather than increased pulsation accounts for the notching of the ribs which is seldom seen in children.

ANSPACH, Chicago.

CONGENITAL MALFORMATION OF THE HEART. DUDLEY E. ROSS and DAVID R. MURPHY, Canad. M. A. J. **61**:114 (Aug.) 1949.

Ross and Murphy present a preliminary report on a method for the surgical treatment of congenital pulmonary stenosis and atresia. Anastomosis of the ascending aorta to the main pulmonary artery was successfully completed in seven dogs. One patient was subsequently operated on and recovered.

MCGUIGAN, Evanston, Ill.

HEREDITARY CYANOSIS. D. M. BOLTZAN and H. SUGARMAN, Canad. M. A. J. **62**:348 (April) 1950.

The case of a 40 year old woman who suffered from profound cyanosis is presented. She had been cyanotic at birth, and other members of the family were known to be affected. No pathological cause was found for the methemoglobinemia. Research disclosed that methemoglobinemia had occurred in her family in a geneologic incidence over four generations. Two of the patient's four children also were found to be cyanotic and to have methemoglobinemia. The condition is definitely hereditary, as a dominant feature.

MCGUIGAN, Evanston, Ill.

RHEUMATIC HEART DISEASE. J. C. BANERJEA, Indian J. Pediat. **16**:57 (April) 1949.

Banerjea gives a detailed report of present day knowledge of rheumatic heart disease.

MCGUIGAN, Evanston, Ill.

BENGAL SPLENOMEGALY. N. G. MOJUMDAR, Indian J. Pediat. **16**:65 (April) 1949.

An unusual form of splenomegaly found in natives of Bengal is described. It presents a definite clinical picture of unknown cause. The disease runs a chronic course but is rarely fatal, and no treatment is known. The patients present irregular fever, abdominal pain and swelling, weakness and anorexia. Examination shows malnutrition, anemia and greatly enlarged spleen and liver.

McGUIGAN, Evanston, Ill.

TARGET CELL ANEMIA: DESCRIPTION OF THREE CASES. GAMAL NOR EL-DIN and A. AWNY, Roy Egyptian M. A. **33**:65, 1950.

Case reports are presented on three patients with target cell anemia. They are considered to be the first three cases reported in Egypt.

McGUIGAN, Evanston, Ill.

PULMONARY FORM OF ACUTE LEUKEMIA IN A GIRL OF THREE YEARS. R. CLEMENT and R. GORMEZANO, Presse méd. **56**:446 (June 23) 1948.

Persistent cough developed in a 3 year old girl. A month later she complained of pains in the feet. Tonsillar swelling and fever appeared, but sulfonamide therapy seemed to help her. Her general condition grew worse, and study of her blood revealed the true condition. Progress was rapidly downhill, and death occurred about 10 weeks after the appearance of the cough.

Postmortem examination showed an extensive involvement of the lungs, with marked infiltration of the leukemic elements into the interalveolar structures.

DAFFINEE, Melrose, Mass.

MULTIPLE AORTIC ANEURYSMS INTRODUCED BY ENDARTERITIS IN A CHILD. D. MORITZ and F. V. GYERGYAY, Helvet. paediat. acta **2**:517 (Dec.) 1947.

The authors report the case of a 14 year old boy who had been under clinical observation for nearly 2½ months. On the basis of symptoms found (relatively increased cardiac dulness, scratching presystolic murmur at the apex of the heart, considerable enlargement of the spleen, protein and erythrocytes in the urine and continually increasing anemia) and roentgen examination, the diagnoses of aneurysm of the aorta and endocarditis lenta were made. At autopsy it was found that the left ventricle was hypertrophic but that the endocardium and the cardiac valves were healthy. In the aorta were two nut-sized aneurysms, separated by an isthmus stenosis with ulcerative inflammation and secondary atherosclerosis. The large cervical and subclavian vessels showed a thromboendarteritis leading partly to total obliteration. The pathological examination revealed a chronic inflammatory tumor of the spleen and an embolic focal nephritis. After sudden loss of consciousness and paralysis of one side, the patient had died in convulsions. The postmortem examination showed the immediate cause of death to be a mycoticoembolic aneurysm of the right middle cerebral artery that had burst, thus causing hemorrhage. On the basis of the summary of clinical and anatomic findings, the case was classified as an endaortitis ulcerosa lenta, induced by aortic aneurysm. Special reference is made to the rarity of vascular changes in childhood and the aortic stenosis as the predisposing factor.

FROM THE AUTHORS' SUMMARY.

A QUICK GRAVIMETRIC METHOD OF ESTIMATING HEMOGLOBIN. PETTER KARLBERG and BO VAHLQUIST, Ann. pædiat. **174**:379 (June) 1950.

The authors describe a quick gravimetric method to determine hemoglobin values (modified after Phillips and Van Slyke). This method should be useful in outpatient departments, child welfare clinics and so forth.

FROM THE AUTHORS' SUMMARY.

STUDY ON THE FRAGILITY OF THE RED BLOOD CELLS. P. TOLENTINO and V. GALLO, Policlinico inf. **16**:365 (Aug.) 1948.

No significant difference was found in the fragility of the red blood cells of persons of three age groups: infants, school children and adults.

HIGGINS, Boston.

THE ROLE OF THE FRAGILITY OF CAPILLARIES IN THE SEASONAL CHANGES OF BLEEDING TENDENCY. Ö. KERPEL-FRÓNIUS, F. VARGA and E. KÁTAI, Orvosi hetil. **59**:249 (Aug. 1) 1948.

Kerpel-Frónius and his co-workers found during their investigations that the change of seasons does not have any effect on the permeability of capillaries but greatly influences their fragility. The winter and spring increase of intracranial hemorrhages and cephalhematomas of newborn infants parallel the decrease of the coagulability of the blood. It seems that the tendency for bleeding is connected not only with vitamin K deficiency but also with the deficiency of vitamin P. The best prophylactic measure in the prevention of bleeding of newborn infants was the prenatal administration of vitamins K and P. This method seems plausible because our diet in the winter and spring months is lacking in vitamins K and P.

GÖRGÉNYI-GÖTTCHE, Budapest, Hungary.

GAUCHER'S DISEASE: A REPORT OF THE FIRST CASE IN CHINA. HUEI-LAN CHUNG, KUANG-YU CH'IN, SUNG-TAO KWAN, HSIN-CHIH WENG and CH'ING-TSENG TENG, Chinese M. J. **66**:119 (March) 1948.

This is probably the first case of Gaucher's disease in China. The patient, a 15 year old Chinese boy, was one of four children. Two siblings, one male, one female, had had abdominal tumors, undiagnosed. The diagnosis of Gaucher's disease was confirmed by puncture of spleen, liver and bone marrow. Splenectomy was performed in 1946, and at the time of the report the patient was still living and in good health.

MACDONALD, Pittsburgh.

MEGLIOCARDIA OF UNKNOWN CAUSE. O. A. DRIESSEN, Maandschr. v. Kindergeneesk. **16**:460, 1949.

Driessen gives a description of a 9 month old girl with a large heart. The possibilities to be considered concerning the cause are discussed.

FROM THE AUTHOR'S SUMMARY.

A CASE OF VIRUS MYOCARDITIS. D. P. R. KEIZER, Maandschr. v. Kindergeneesk. **16**:475, 1949.

Keizer gives a description of a case of acute virus myocarditis in a boy of 5 years.

FROM THE AUTHOR'S SUMMARY.

CHRONIC COMPRESSION OF THE HEART DUE TO AN EXUDATIVE PERICARDITIS. J. I. DE BRUIJNE, Maandschr. v. Kindergeneesk. **17**:305, 1950.

The case history of a 4½ year old child presenting symptoms of chronic compression of the heart is described. Operation revealed the cause of the compression to be an exudative pericarditis instead of constrictive pericarditis, as had been expected. At a second attempt to relieve the chronic compression of the heart, a large part of the anterior portion of the pericardium was removed. The child's condition became gradually worse, and she died 2½ years after the onset of the illness. The cause of the disease was not cleared up. Postmortem examination revealed chronic inflammation of the endocardium. The clinical symptoms were supposed to be due to the chronic pericardial effusion, complicated by insufficiency of the degenerated heart muscle.

FROM THE AUTHOR'S SUMMARY.

SPLEEN AND ANEMIA. S. VAN CREVELD, Nederl. tijdschr. v. geneesk. **91**:416 (Feb.) 1947.

A boy of nearly 3 years of age showed paleness and splenomegaly, with anemia, leukopenia and thrombopenia, normal resistance of the red blood cells to hypotonic salt solutions, free hydrochloric acid in the gastric juice, no increase of urobilinogen in urine and stool, no symptoms of obstruction of the splenic vessels and nothing remarkable on the roentgenogram of the bones.

Therapy with iron, liver extracts and blood transfusions had no result. The child recovered quickly after splenectomy. Pathologic examination showed no obstruction of the vessels of

the spleen. Microscopic examination of the spleen revealed chronic congestion with fibroadenia. The liver was normal. If congestion is caused by obstruction outside the spleen, the disturbance of the blood picture is limited. In cases of congestion of the spleen without this obstruction, hypochromic anemia, mostly leukopenia and sometimes also thrombopenia are found.

Doan distinguishes three systems in the spleen: the vascular, the lymphatic and the reticuloendothelial. The last-mentioned system is of great value in the formation and destruction of the blood cells.

Disturbances in this system may result in hemolytic icterus, thrombopenia, thrombopenic purpura (morbus maculosus werlhofii), primary splenic neutropenia and primary splenic panhematopenia. The anomalies may be congenital or acquired.

The boy described may be regarded as having primary splenic panhematopenia. The symptoms he showed are typical of this disease. A case of secondary splenic panhematopenia in a girl with acholuric jaundice is also briefly described.

Doan recommends the epinephrine test for the differential diagnosis of aplastic or hypoplastic anemia. Injection of epinephrine is followed by an increased number of blood cells in cases of primary splenic panhematopenia.

FROM THE AUTHOR'S SUMMARY.

Diseases of Nose, Throat and Ear

GLIOMA OF THE NOSE: REPORT OF A CASE OF THE EXTRANASAL TYPE. J. H. HILL, Arch. Path. **48**:183 (Aug.) 1949.

A case is reported of a newborn infant who was found to be normal except for a dome-shaped mass on the left side of the bridge of the nose. The bridge was not widened. The tumor was removed at 6 days of age when no increase in size had occurred. There was no recurrence after eight months, and the scar was not noticable. Microscopically the tissue consisted of corium of the skin occupied by glial tissues which extended to all margins of excision. The author believes that the tumor arose from ectopic brain tissue separated from the main source by an anomaly of development in early life and that it was derived by herniation of the tissue through the enclosed edges of the frontal bone, with complete separation from the brain through later closure of the bones.

HAW CHAN, San Francisco.

CLINICAL NOTE ON STUTTERING AND CLUTTERING IN YOUNG CHILDREN. KATRINA DE HIRSCH and WILLIAM S. LANGFORD, Pediatrics **5**:934 (June) 1950.

The early clonic iterations of the child between 20 and 40 months are a part of the normal speech patterns of growing children. As a rule, reassurance of the parents and withdrawal of attention and concern from speech are all that is necessary.

There is a group of children who start speaking late and whose familial background shows evidence of difficulty in the language area and delay in establishing a functional superiority of one side over the other. Many of these children have trouble with the enunciation of specific sounds, with vocabulary and with sentence construction. In spite of at least average intelligence, these children handle speech poorly. They often show a great number of clonic iterations at an age when most children have already discarded them. Their handling of speech closely resembles the cluttering of older children and adults. Such children frequently need technical help with sounds, vocabulary and grammatical construction. Smoother production of speech and slowing up of speed will often bring about a reduction in the original iterations. The pediatrician should be aware of the fact that emotional tensions and conflicts tend to become fixed to a speech mechanism which is none too stable in these children. The cluttering child may easily turn into a stutterer.

There is a larger group of children who show no familial difficulty in the language area, who talk early and quite well and who abruptly begin to stutter at some time during childhood. Some of these children display other symptoms of emotional disorder; others seem to function effectively in most areas but express their emotional conflicts principally in stuttering. These children should be referred for psychiatric help early.

For older children who stutter, a careful differential diagnosis is necessary as to the relative importance of specific language and emotional factors in pathogenesis. If existing emotional difficulties seem to be the result rather than the cause of the stuttering, a more specifically technical therapy is favored; in cases in which emotional factors are outstanding, a psychiatric approach is to be preferred.

Speech is a means of expression of the personality as well as a means of communication; severe dysfunctions in speech may reflect a personality disorder or a disorder of interpersonal relations or both. In the child, however, speech is also a tool which he masters as it develops. A speech difficulty in the growing child must be evaluated from both points of view.

FROM THE AUTHORS' SUMMARY.

THE BELL REDUCED VISIBLE SYMBOL METHOD FOR TEACHING SPEECH TO THE DEAF. JAMES H. PLATT, Speech Disorders **12**:381 (Dec.) 1947.

A review is given of the symbols developed by A. Melville Bell for the use of the deaf and the hard of hearing in learning speech. Platt concludes that the Bell reduced visible symbol method was successful for the following reasons: 1. It was developed from the outlines of various speech organs, thereby permitting the deaf student to visualize better the speech positions. 2. The basic symbols were simple and easy to remember. 3. It was relatively easy to combine the basic symbols in such a way as to represent adequately the various sound positions. 4. Because of the necessity for the deaf student to become familiar with the speech anatomy, even though superficially, he would be likely to be influenced by this method to take an objective viewpoint concerning his disorder.

PALMER, Wichita, Kan.

MALIGNANT NASOPHARYNGEAL TUMOR WITH EXOPHTHALMOS. D. G. VULLIAMY, Proc. Roy. Soc. Med. **41**:452 (July) 1948.

Vulliamy reports the case of a patient, aged 4 years who was quite well until whooping cough developed in July 1947. In August 1947 there was slight trauma to the left knee, after which tenderness of the lower third of the femur developed, with pyrexia. Blood culture yielded Staphylococcus aureus. Acute osteomyelitis was diagnosed at Dartford Hospital. Roentgenograms of the femur were then normal, and pyrexia responded to penicillin. A glazed look of the eyes was noticed by the parents at this time (? onset of blindness). A month later the child became drowsy, lost his appetite and complained of headache. Gradually increasing exophthalmos was noticed. There was increasing blindness with optic atrophy in the right eye and papilledema of the left. The child was thought to have retro-orbital neoplasm. There were tenderness over the long bones and bloody discharge from the right nostril.

WILLIAMSON, New Orleans.

STENOSIS OF THE RESPIRATORY PASSAGES FROM PHLEGMONOUS INFLAMMATION PRIMARILY LOCALIZED IN THE EPIGLOTTIS. G. DOLIVO, Helvet. paediat. acta **2**:397 (Nov.) 1947.

Six cases of stenosis of the respiratory tract which were caused by a primary phlegmonous inflammation of the epiglottis are described. The extremely rapid and often fatal course of the disease demands an early diagnosis. The examination of the larynx makes a rapid differential diagnosis possible. From the onset antibiotics must be administered in maximal doses. Tracheotomy is the method of choice and should be performed as soon as severe dyspnea occurs.

FROM THE AUTHOR'S SUMMARY.

IMPORTANCE OF ADEQUATE STUDY AND TREATMENT OF SPEECH DEFECTS IN CHILDREN. G. BELLUSSI and E. FAGIANO, Pediat. Med. prat. **23**:166 (Aug.) 1948.

A statistical study is presented of the cases of speech defects seen in the speech clinic at the University of Turin. Of 460 children, 310, or 67 per cent, were boys. The number of stammerers was 243, or 53 per cent of the total. In 55 of the cases of stammerers another member of the family had a speech defect. The stammering dated back to the period of

beginning speech in 24 per cent of the cases, to the preschool ages of 2 to 6 years in 59 per cent and to the period when the children were already in school in only 17 per cent. Sigmatism was the next most frequent speech defect found, occurring in 11 per cent of the cases.

HIGGINS, Boston.

PERSISTENT AND RECURRING DYSPHONIA FROM LARYNGITIS. E. PALLESTRINI, Policlinico inf. **16**:419 (Sept.) 1948.

Dysphonia in laryngitis is due to the failure of the true cords to maintain sufficient vibrations to give a pure note. Furthermore, there is failure of the two cords to vibrate in unison. This condition is very prone to occur in children with large adenoids or thymicolymphaticus and between the ages of 2 and 7 years, when the development and functional activity of the larynx are at their maximum.

HIGGINS, Boston.

ETHMOIDITIS IN THE INFANT. AMALIO FERNANDEZ-DELGADO DE LA PENA, Acta Pediat. españ. vol. 85 (Jan.) 1950.

The author discusses the fact that rhinitis and similar apparently mild infections may become extremely serious and that many cases of ethmoiditis in children are diagnosed only at autopsy. The immaturity of the bone development of the ethmoid sinuses and surrounding bony structures favors the spread of the infection from the nose to the ethmoid sinuses and also to the postorbital region. Too much importance cannot be attached to the clinical symptoms of edema of the eyelids or tumor formation at the mesial aspect of the eye.

While these symptoms may not be serious in an adult and roentgenography and transilluminination may help with diagnosis, this is not practical in small infants. Hence, one should suspect ethmoiditis if rhinitis is accompanied with swelling of the eyelids with or without copious nasal discharge.

Many patients have spontaneous cure, but in some meningitis develops and the mortality is high. The author reviews the cases of six patients under his care, all of whom were under 1 year of age. All had meningitis, and cultures of the spinal fluid showed two with meningococcic meningitis, two with streptococcic infections and two with infections due to Bacillus hemophilus influenza. Two of the children lived, and the author says that penicillin and streptomycin gave best results, regardless of the bacteriologic findings on spinal fluid cultures.

ALLEN, Santa Fe, N. Mex.

BIOLOGIC DIAGNOSIS AND EVALUATION OF THE ACTIVITY OF THE TONSIL FOCUS BY MEANS OF "TONSIL PUNCTURE." BERNFRIED LEIBER, Med. Klin. **44**:797 (June 24) 1949.

Leiber describes the method of "tonsil puncture." Material is aspirated with a trocar and suspended in 5 ml. of sterile isotonic sodium chloride. Then 0.1 ml. of the suspension is injected intracutaneously. At the same time a control injection is made with the isotonic sodium chloride. Before the injection and 72 hours after it differential blood counts are made. The skin reaction is read after 24 and 48 hours. On the day before and the day after the injection the body temperature is taken hourly until, in case of a febrile reaction, the norm is reached. The tonsil as a source of a focal infection is indicated by a positive skin reaction, a considerable increase in eosinophils, a considerable relative lymphocytosis 72 hours after the injection, a relative monocytosis which is not a constant symptom and a febrile reaction within the first hours after the injection. Numerous general reactions and a focal reaction such as double-sided neck pains may be observed. Often all reactions are more or less pronounced, at other times only a few. The intensity of the reactions and the kind, as for instance the absence of a good eosinophilia, are of aid in determining when a tonsillectomy is to be performed.

AMBERG, Rochester, Minn.

TONSILLITIS CHRONICA AND FOCAL INFECTION. R. MITTERMAIER, Med. Klin. **45**:553 (May 5) 1950.

Mittermaier describes the lesions characterizing chronic tonsillitis and reviews the methods for diagnosis of the disease. He then discusses the significance of chronic tonsillitis as a possible source of focal infection.

AMBERG, Rochester, Minn.

COCHLEAR AND VESTIBULAR EXAMINATION AFTER STREPTOMYCIN TREATMENT. E. H. MAJER, Wien. klin. Wchnschr. **60**:844 (Dec. 31) 1948.

Of 40 patients, mainly children, with tuberculous meningitis or miliary tuberculosis who were treated with streptomycin, only four had a slight reduction of the higher tone limit, indicating a cochlear lesion. Nearly all patients had vertigo and disturbances of equilibrium which disappeared after a few weeks or months. Children treated with large doses of streptomycin gave evidence of vestibular disturbance; in 80 per cent this was manifested as decreased or absent caloric irritability.

AMBERG, Rochester, Minn.

RESULTS OF TONSILLECTOMY IN CHILDHOOD. F. BÁNHIDY, Orvosok lapja **4**:253 (Feb. 22) 1948.

A review of numerical data giving the results of a considerable number of cases shows without any doubt that diseased tonsils exercise an effect, directly and indirectly, on the organism and maintain a condition which interferes with the normal physiological development of the child. For this reason it is necessary that in the public health services the condition of the larynx and the nose of children should be regularly checked.

GÖRGÉNYI-GÖTTCHE, Budapest, Hungary.

OTITIS IN INFANTS. P. KLAUCO, Paediat. danub. **5**:249 (April-May) 1949.

Among the 2,349 infants under 2 years of age admitted to the Department of Paediatrics of Bratislava University in 1946, there were 500 with otitis, an incidence of 21.3 per cent. Of these, 40 (8 per cent) died, mostly as a result of complications; 22 (4.4 per cent) were discharged in an unchanged state, and the rest recovered. Antrotomy was performed on 92 patients. Of these, 20 (21.7 per cent) died. Mastoiditis and other complications could be prevented in most cases by chemotherapy, penicillin and transfusions. Conservative treatment of mastoiditis is condemned. To achieve real success, antrotomy must be performed before irreparable lesions of the liver and other organs have developed. Great caution is advised for grave toxic states, as any aggravation of the condition following operation, may lead to death.

FROM THE AUTHOR'S SUMMARY.

CHANGES IN THE PROTEINS OF THE BLOOD PLASMA IN SERIOUS OTOMASTOIDITIS OF INFANTS AND THEIR IMPORTANCE FOR THERAPY. A. PALACKÝ and R. STRÝCEK, Pediat. listy, 1949, no. 3, p. 97.

In 93 cases of infantile otitis and mastoiditis the proteins of the blood plasma were examined. In 69 of the serious and complicated cases a hypoproteinemia, caused by the reduction of globulin, with proteins under 5.5 per cent, was found. The reaction of Weltmann proved to be important diagnostically as well as prognostically in the nephelometric reading according to the method of Wuhrmann and Sunderly. The hypoproteinemia was improved by blood or plasma transfusions and by implantation after the method of Filatov.

FROM THE AUTHORS' SUMMARY.

Diseases of Lungs, Pleura and Mediastinum

LOEFFLER'S SYNDROME WITH SKIN MANIFESTATIONS. ALBERT M. JONES and EVELYN B. OGLE. J. Pediat. **36**:505 (April) 1950.

Jones and Ogle report a case of Löffler's syndrome associated with urticaria. The urticaria occurred early in the course of the disease. Roentgen evidence of pulmonary involvement persisted for several weeks after the urticaria disappeared.

MACDONALD, Pittsburgh.

BRONCHIAL ASTHMA IN CHILDHOOD. J. DUDLEY YOUMAN, New Orleans M. & S. J. **102**:387 (Feb.) 1950.

So-called asthmatic bronchitis is considered by Youman to be perennial rhinitis with subclinical allergic asthma. He urges control of the allergy, which is usually due to one of the inhalants, with concurrent treatment of the infection.

McGUIGAN, Evanston, Ill.

APLASIA OF THE UPPER AND MIDDLE LOBES OF THE RIGHT LUNG WITH HYPOPLASIA OF THE LUNG ARTERIES AND DEXTROCARDIA. M. VEST, Ann. pædiat. **173**:65 (Aug.) 1949.

The various diagnostic signs which point to agenesis or hypoplasia of one lung are discussed. This is followed by the description of a case of a boy of 9 months in whom agenesis of the upper and middle lobes of the right lung was complicated by a blind-ended upper lobe bronchus, hypoplasia of the pulmonal artery leading to these parts and dextrocardia. After a review of the literature is given, the etiology and pathogenesis of such malformations are discussed.

FROM THE AUTHOR'S SUMMARY.

THE PROGNOSIS OF BRONCHIECTASIS IN CHILDHOOD. H. WISSLER and MARIE-LOUISE HOTZ, Helvet. pædiat. acta **3**:475 (Dec.) 1948.

Thirty-eight patients who had bronchiectasis in childhood were reexamined six to 15 years after the first treatment. Of these, 9 had died, 24 were in good health and had few symptoms (5 of them had had surgical treatment) and 5 were in unsatisfactory condition. These facts should be considered when the indication for lobectomy in childhood is discussed.

FROM THE AUTHORS' SUMMARY.

AEROSOL TREATMENT IN SOME INFECTIONS OF THE RESPIRATORY TRACT. G. CALZETTI, Lattante **19**:534 (Sept.) 1948.

Two infants with pyopneumothorax responded favorably to aerosol penicillin therapy when other means of administering antibiotics had not cleared up the condition. Another infant with a bronchial fistula following empyema was treated prophylactically with aerosol penicillin until the fistula closed.

HIGGINS, Boston.

AEROSOLS OF PENICILLIN IN SOME DISEASES OF THE RESPIRATORY TRACT OF CHILDREN. U. PELLEGRINI, Lattante **20**:140 (March) 1949.

Clinical benefit followed the administration of penicillin by aerosol in cases of tonsillitis, laryngitis, bronchitis, asthma and bronchopneumonia. In cases of bronchiectasis and lung abscesses this treatment lessened the amount and the odor of the sputum. Aerosol penicillin has also been found of prophylactic value for patients about to undergo lung surgery.

HIGGINS, Boston.

PENICILLIN BY THE ENDOPLEURAL ROUTE IN THE CURE OF ACUTE PULMONARY INFECTIONS OF INFANTS. T. PORCELLI, Lattante **20**:146 (March) 1949.

In 20 severe cases of bronchopneumonia, in five of which the disease was resistant to sulfathiazole and/or intramuscular penicillin therapy, the giving of penicillin intrapleurally was followed by a rapid recovery of the patient.

HIGGINS, Boston.

FAMILIAL PRIMARY ATYPICAL PNEUMONIA. ROBERTO RAMOS MOTILLA and CARLOS V. GAITÁN, Bol. méd. d. Hosp. inf., México **5**:838 (Dec.) 1948.

The authors present the case histories of three brothers suffering from primary atypical pneumonia. Patients 2 and 3 were possibly infected from patient 1, since their illnesses began seven and nine days later respectively.

The data which suggested the diagnosis were familial history, healing of the disease with a minimal state of toxemia, pertussoid, abundant crepitant and subcrepitant rales of basal predominance and progress not modified by sulfonamide or penicillin treatments.

The laboratory data which favored the diagnosis were leukopenia in two of the cases and moderate leukocytosis in the third, with slight neutrophilia in all three; normal urine; sterile bronchial secretion culture, and chest roentgenograms typical of the disease.

Treatment was symptomatic, and healing took place in a period of 10 to 15 days.

It was not possible to investigate the virus or complement fixation.

FROM THE AUTHORS' SUMMARY.

STAPHYLOCOCCIC EMPYEMA. FRANCISCO PARADA and RAUL HERNANDEZ. Rev. chilena de pediat. **19**:251 (March) 1948.

The authors report 11 cases of staphylococcus pleural empyema. They analyze the frequency of the disease in the period of 1941 to 1947 and compare the cases occurring in this period in the Hospital Roberto del Río with those of the years 1929 to 1940.

A review of the national and foreign literature about empyema, especially that of staphylococcus origin, is given. The authors report their experience concerning the prognosis and the treatment of the infection.

FROM THE AUTHORS' SUMMARY.

A CASE OF VERY EXTENSIVE SUBCUTANEOUS EMPHYSEMA AFTER SLIGHT INFECTION OF THE RESPIRATORY TRACT. TAN KIAN GWAN, Maandschr. v. kindergeneesk. **16**:59 (Feb.) 1948.

In a 4 year old boy there developed, after a slight infection of the respiratory tract, an extreme subcutaneous emphysema of the face, neck, chest, abdomen, scrotum and legs. The alarming symptoms due to mediastinal emphysema disappeared in a few days. Until 20 days after admission to the hospital, the emphysema in the scrotum was demonstrable. The therapy consisted solely in administration of sulfadiazine for a few days.

VAN CREVELD, Amsterdam, Netherlands.

Diseases of the Gastrointestinal Tract, Liver and Peritoneum

GALACTOSE DIABETES (GALACTOSEMIA): A CLINICOPATHOLOGIC STUDY OF TWO SIBLINGS. LEO S. BELL and WILLIAM C. BLAIR, J. Pediat. **36**:427 (April) 1950.

The authors review the literature on this subject and report two new cases of galactosemia in siblings. From studies of the livers of these two patients, the authors suggest that infiltration of the liver with fat, rather than with glycogen, is the basic cause of the hepatic enlargement and dysfunction. They also present evidence that the excessive fat in the hepatic cells may accentuate the inability of the liver to metabolize galactose normally. In addition to a lactose-free diet, they suggest the use of choline and methionine in treatment.

MACDONALD, Pittsburgh.

PEPTIC ULCER IN INFANCY AND CHILDHOOD. ROBERT B. TUDOR, Minnesota Med. **33**:57 (Jan.) 1950.

The subject of peptic ulcer in infancy and childhood has been reviewed, and a total of 286 cases are reported, three of them being the author's own cases. Of this number, in 218 the ulcers were duodenal and pyloric and in 68 gastric. Ulcers of the newborn have special characteristics. The majority bleed profusely or perforate. In many infants the onset is sudden, without the usual symptoms or signs. After the first month of life and for the remainder of the infancy period the majority of ulcers bleed grossly or perforate but there are usually premonitory symptoms, such as abdominal pain, vomiting, bloody emesis and melena or persistent pylorospasm. Between the ages of 2 and 6 examples of peptic ulcers are rare. After this age hemorrhages are less likely to occur. In a series of cases reported bleeding occurred in 48 per cent of children under 1 year of age and in 29 per cent of the total series.

STOESSER, Minneapolis.

STAPHYLOCOCCUS AUREUS IN AN OUTBREAK OF INFANTILE DIARRHEA. HARVEY B. LYON and LOWELL A. RANTZ, Pediatrics **5**:617 (April) 1950.

True infectious diarrhea caused by Staphylococcus aureus in the newborn infant has been reported. In these infants large numbers of this organism were present in the fecal flora. The epidemic described by Lyon and Rantz was of this type.

Staphylococci were recovered, usually in large numbers, from the stools of seven of nine infants affected. Technical difficulties may have prevented the isolation of this organism for the one additional infant. This high rate of recovery from diarrheal stools strongly suggests that Staph. aureus was the etiologic agent of the disease. A control study not reported in the paper in detail was conducted; in it serial stool cultures were obtained for 20 healthy babies. Staph. aureus was recovered on only one occasion by direct inoculation of feces on blood agar plates, which demonstrates that this organism is rarely present in the normal fecal flora of infants.

The disease itself was mild. Dehydration and disturbances of electrolyte balance did not occur. The diarrhea ran its course in two to three days. Treatment with dihydrostreptomycin was instituted. This drug was used because recent reports indicate that hospital infection by Staphylococcus is likely to be caused by organisms highly resistant to the action of penicillin. Such strains are regularly inhibited in vitro by streptomycin. Administration of the drug was associated with the prompt disappearance of staphylococci from the stools. The effect of this therapy could not be evaluated, since the disease was self limited. Patients who did not receive antibiotic therapy did not have a more prolonged course or severer illness.

FROM THE AUTHORS' SUMMARY.

CHRONIC CHOLECYSTITIS IN CHILDHOOD. EUGENIO CIENFUEGOS, HAYDEE SEPULVEDA and ENRIQUETA BARILARI, Rev. chilena de pediat. **19**:802 (Oct.) 1948.

A study is made of 71 cases of chronic cholecystitis studied at autopsy. The cases were of children in whom a histological examination revealed lesions of chronic cholecystitis.

Thirty-five of the instances of lesion were found among 100 autopsies done routinely, and 36, in autopsies in which the gallbladder macroscopically evidenced a chronic lesion.

Most of the cases were seen in children under 5 years old and a majority of these in young infants between 7 days and 1 year of age (45 per cent).

In many cases (14 per cent) an altered constitutional type were found, and in all cases, a marked undernutrition with a dysergia that facilitated infections among which the respiratory infections seemed to be terminal.

In this study all patients arrived at the hospital in a very poor general condition; 26 per cent died during the first 24 hours, and 77 per cent, before the tenth day; thus a complete study could not be done.

The most frequently found symptoms were vomiting, diarrhea, splenohepatomegaly, jaundice and purpura. In this article the differential diagnosis with many other diseases that produce abdominal symptoms is considered. The national and foreign bibliography on this subject is revised.

The authors estimate that given the frequency with which cases with similar symptoms, especially if pain can be elicited with its characteristic localization, can be found, the possibility of an acute, subacute or chronic gallbladder disease should be kept in mind. The authors' investigations guided them in that direction.

The routine blood and stool examinations, a gastric juice analysis and a duodenal drainage are of primary importance.

The duodenal drainage not only permits a study of the bile obtained but it also may be of therapeutic value.

The liver function tests permitted study of the possible damage done to the liver parenchyma.

FROM THE AUTHORS' SUMMARY.

GASTRIC DUODENAL ULCER IN THE CHILD. EDMUNDO CARDEMIL, PEDRO OYARCE and MANUEL NEIRA, Rev. chilena de pediat. **21**:114 (March) 1950.

The authors present five case histories of children 4, 4½, 6, 8 and 14 years old with peptic ulcers. Diagnosis for the first two children was made at autopsy, for another clinically and for the other two roentgenologically. The authors review the literature, compare statistics and conclude that peptic ulcers are present in infancy with a greater frequency than is generally realized. They analyze 4,096 autopsies of children from birth to 12 years of age that were hospitalized at the Roberto del Rio Hospital between the years 1932 and 1949 and find chronic nonspecific peptic ulcers even in children 4 years old, a diagnosis that during life is confirmed only roentgenologically. To corroborate the latter statement they mention the fact that among 49,938 patients admitted to the same hospital, not once was this diagnosis made.

The authors classify the ulcers as in the acute, secondary and chronic or primary stage. The first type, characteristic of infancy, are secondary to infections, intoxications and metabolic disturbances or are associated with pyloric stenosis or with Meckel's diverticulum. In older children the ulcers are found to be associated with chronic nutritional disturbances and caused by prolonged malnutrition. The authors report two cases that they believe have this origin.

The cause of the chronic ulcer in children is even more complex than in adults, and a great percentage of ulcers in children date from infancy.

The authors analyze the symptomatology which is very meager in infancy but later in childhood is manifested by the following triad: pain, vomiting and anorexia. Hyperchlorhydria is seen more frequently in older children, and in approximately 40 per cent of the children there is an accompanying hematemesis.

The diagnosis is made when in the presence of these symptoms there is a confirming gastric series. There is not yet sufficient experience to make a statement concerning prognosis.

Treatment is preferably medical, except for a possible perforation. Rest and restricted diet are the essential parts of the treatment. The diet should be one that does not produce excessive secretions or motor activity, and the patient should be kept on it until a roentgenogram indicates healing. The ideal food is milk with supplements of carbohydrates and cream. In most cases it is unnecessary to resort to other forms of therapy.

FROM THE AUTHORS' SUMMARY.

ON BLOOD CHANGES IN LIVER DISEASE IN INFANCY: ON MACROCYTIC HYPERCHROMIC ANEMIA IN CONGENITAL ATRESIA OF THE BILE DUCTS. EUGENE STRANSKY and DOMICIANA DAUIS-LAWAS, Ann. pædiat. **173**:151 (Sept.) 1949.

Infectious hepatitis in infancy is accompanied with a more or less marked anemia. The anemia develops as a consequence of hepatitis and may be absent in the early stage. It may be macrocytic or microcytic, hyperchromic or hypochromic. In the authors' restricted experience, they could not find a definite type. Unlike infectious hepatitis, in congenital atresia of the bile ducts there is soon an anemia which is always macrocytic, while it may be hyperchromic, hypochromic or both (diphasic). The macrocytic anemia in infectious hepatitis as well as in congenital atresia of the bile ducts is not accompanied with megaloblastic reaction or impaired maturation of the erythrocytes in the bone marrow, although it improves very fast if folic acid is administered. The fact that hypoproteinemia and hunger edema are frequently accompanied with macrocytic anemia without hyperchromia and definitely without megaloblastosis may play an important role in the development of macrocytic anemia in liver diseases, including congenital atresia of the bile duct.

The authors did not discuss liver cirrhosis in their paper as they had had thus far no chance to observe liver cirrhosis in the first year of life.

FROM THE AUTHORS' SUMMARY.

THE RELATION BETWEEN ACETONEMIC VOMITING AND MIGRAINE. BO VAHLQUIST, Ann. pædiat. **173**:272 (Oct.) 1949.

From the author's observations made on 24 cases of cyclical vomiting and from information gained from five descriptive case histories, he reaches several conclusions.

In a small proportion of patients with cyclical vomiting there seemed to exist a direct connection between these attacks and migraine. There was either an alternation between

attacks of cyclical vomiting and migraine or the former were caused by true attacks of migraine in which the initial headaches were less preponderant while the tendency toward vomiting was more marked than usual.

A large group of patients with cyclical vomiting gave histories of migraine among relatives.

A comparatively large group of patients with cyclical vomiting did not give a history of migraine among relatives and were not affected by this disease themselves. The author states, however, that the average age at the last examination of his patients was 14 years and that it would be possible, of course, that some of them would manifest migraine later in life. The connection with migraine in this group of patients was quite uncertain. It cannot be altogether excluded, however, since signs of neurolability were often present, and migraine itself may occasionally arise in persons without a typical family history.

FROM THE AUTHOR'S SUMMARY.

TREATMENT OF POSTOPERATIVE HICCUP DUE TO ACIDOSES WITH SODIUM BICARBONATE. M. WENZL, Wien. klin. Wchnschr. **61**:600 (Sept. 16) 1949.

In some cases the alkali reserve was reduced after operation. Persistent hiccuping decreased within 24 hours in six cases and stopped in 48 hours on peroral administration of a sodium bicarbonate solution. Within two hours 18 Gm. of sodium bicarbonate was given, and this dose was repeated the next day. If peroral administration is not feasible, the drug can be given intravenously.

AMBERG, Rochester, Minn.

GASTRIC POLYP WITH GLANDULAR INVOLVEMENT IN THE NURSLING. JOSEF VANEK, Pediat. listy **4**:11, 1949.

In an infant girl, aged 5 weeks, who had suffered from vomiting since birth, the postmortem examination showed a flat polypous growth situated in the prepyloric antrum approximately 1 cm. above the pylorus. The growth consisted of a considerably hypertrophied mucosa which bulged toward the lumen as a double fold. The basal portions of the glands penetrated in some places into the submucosa, and similar glandlike tubules were found in the muscularis propria, reaching as far as the subserosa. Many of them were dilated, thus forming small cysts which contained chiefly mucus. The epithelial lining, although flattened in the cysts, had a typical appearance everywhere and consisted of one layer of columnar or cuboidal cells, for the most part containing mucus. The glands were surrounded by fibrous tissue arranged circularly; there was no trace whatsoever of inflammatory reaction. The condition, though highly suggestive of adenocarcinoma, is not considered as such but is believed to be a congenital malformation. A similar finding in the resected pylorus of a man is mentioned. Of the three cases cited by Bormann as the only instances of carcinoma in nurslings it was found that none could be accepted as genuine. As to the case of Kaulich, concerning an infant aged 1½ years (not 6 months, as Bruning-Schwalbe's manual has it), this is a second-hand quotation, the actual author of which is not given. It can be concluded, therefore, that no case of carcinoma of the stomach has been so far seen in a nursling.

FROM THE AUTHOR'S SUMMARY.

LIVER CIRRHOSIS IN INFANTS. A. DEKKER-JONKER, Maandschr. v. kindergeneesk. **16**:465, 1949.

Familial lipomatosis of the liver with beginning of cirrhosis is described. Two children in one family died at the age of 1½ months and 18 days, respectively; they both had glycosuria. The etiology, the literature and the possibility of use of a protein-rich diet for the mother and the child during and after the next pregnancy are discussed.

FROM THE AUTHOR'S SUMMARY.

THE CELIAC SYNDROME. YMKJE M. TRAP, Maandschr. v. kindergeneesk. **16**:469, 1949.

The author gives a description of a case of a girl 11 months of age suffering from the celiac syndrome.

In this case the origin could be a slight fibrosis of the pancreas. Excellent results were achieved after folic acid therapy.

FROM THE AUTHOR'S SUMMARY.

SURGICAL TREATMENT OF IDIOPATHIC MEGACOLON. CHR. VAN GELDEREN, Maandschr. v. kindergeneesk. **16**:504, 1949.

Based on the successful treatment of two patients, a plea is made for the operative treatment (sympathectomy) of idiopathic megacolon. In the first patient, a 19 year old youth, extirpation of the superior hypogastric plexus and lumbar sympathectomy were done. In the second patient, a 12 year old boy, only lumbar sympathectomy was done. The indication for this operation was furnished by functional examination, performed by administering a parasympathetic drug carbachol (doryl®), by measuring the pressure in colon and bladder after filling of these organs and by giving segmental spinal anesthesia. The first patient's bladder was atonic. Injection of carbachol was followed by an increase of bladder pressure as well as by contraction of the intestine.

The second patient's bladder was not atonic and therefore extirpation of the hypogastric plexus was not deemed necessary. Operation was followed, in both cases, by subjective and objective improvement, the size of the sigmoid being decreased considerably when examined roentgenologically.

VAN CREVELD, Amsterdam, Netherlands.

ASPIRATION BIOPSY OF THE LIVER IN CHILDREN. C. VAN BEEK and A. J. C. HAEX, Maandschr. v. kindergeneesk. **17**:111, 1949.

After a short discourse concerning the methods and results of aspiration biopsy of the liver (after the method of Iversen and Roholm) the contraindication of use of this procedure in children is critically reviewed.

FROM THE AUTHORS' SUMMARY.

Diseases of Ductless Glands; Endocrinology

A CASE OF THE LAURENCE-MOON-BIEDL-BARDET SYNDROME IN INFANCY. W. SCHÜRER, Ann. pædiat. **173**:129 (Sept.) 1949.

This is a description of a case of Laurence-Moon-Biedl-Bardet syndrome observed in an infant. Particularly impressive were the excessive obesity, the increased length of the child and the deafness. In addition, changes in the fundi were found as well as anomalies of bone development, lowered basal metabolic rate, slight disturbances of the carbohydrate metabolism, hypochloremia and hypertension.

There followed a discussion of the syndrome that in the light of present day knowledge must be considered to be a recessive inheritance. On the other hand, after observing the metabolic symptoms and the intelligence defect, the author is of the opinion that part of the symptoms can be explained by a damage to the mesencephalon during the early fetal life.

FROM THE AUTHOR'S SUMMARY.

THERAPY OF COMA DIABETICUM WITH COCARBOXYLASE: EXPERIMENTAL AND CLINICAL RESULTS. S. MARKEES and F. W. MEYER, Schweiz. med. Wchnschr. **79**:931 (Oct. 1) 1949.

In experiments on rabbits with alloxan diabetes it was shown that on administration of sodium pyruvate the destruction of pyruvic acid in the blood is delayed, in comparison with normal rabbits, while the pyruvic acid content of the blood before injection is not increased above normal. This happens when the diabetes is stationary or reversible. Under these conditions thiamine is capable of correcting this delayed decomposition. When the diabetes is severe, thiamine, as such, cannot do so any longer. In these cases the pyruvic acid of the blood is increased, but it can be reduced by administration of cocarboxylase. Recovery of rabbits from coma of severest diabetes was possible under treatment with cocarboxylase, riboflavin and insulin. The blood of normal humans contains about 0.81 mg. per 100 cc. of pyruvic acid. It is about the same in cases of compensated diabetes, in which on administration of sodium pyruvate the decomposition is delayed. In one case during a state of precoma and coma an increase of pyruvic acid up to 5.2 mg. per 100 cc. was noted. In the blood of two children with diabetic coma the values for pyruvic acid were 2.38 and 3.08 mg. per 100 cc.

The delayed decomposition could be converted with thiamine plus riboflavin. Patients in diabetic coma recovered from it sooner when, besides treatment with large doses of insulin and fluid, cocarboxylase was given intravenously in a dose of 100 mg. or more and 20 mg. of riboflavin was given intramuscularly. On the patient's relapse into coma and on persistence of deep acidosis the injections are repeated. Under this treatment the alkali reserve increases more rapidly. This treatment is of benefit in addition to insulin and fluid therapy; however, it cannot replace insulin.

AMBERG, Rochester, Minn.

USE OF PURIFIED (RECRYSTALLIZED) INSULIN PREPARATION IN CASES OF INSULIN ALLERGY. E. SCHWARZ and F. KOLLER, Schweiz. med. Wchnschr. **79**:936 (Oct. 1) 1949.

Three patients with general and localized insulin hypersensitization tolerated a preparation of insulin which was five or seven times recrystallized.

AMBERG, Rochester, Minn.

HYPERPARATHYROIDISM. F. MERKE and O. SCHÜRCH, Bull. Schweiz. Akad. d. med. Wissensch. **5**:244 (July) 1949.

Six cases of hyperparathyroidism caused by adenomas of the parathyroid glands are briefly described. They present a pronounced variation in symptoms. In three cases the skeleton only has been involved (in one case, minimal involvement). In the remaining cases besides the skeletal involvement there were present renal calculi (two cases) or nephrocalcinosis (one case). One case with minimal skeletal involvement showed a toxic gastritis (very frequent vomiting) and a "pseudo diabetes insipidus" (involvement of the posterior pituitary gland). In four cases one adenoma and in one case two adenomas could be removed by operation. All the patients recovered. In one case the adenoma could not be found at the first operation; the patient did not recover and is still receiving treatment.

At least some of the problems concerning the hyperparathyroidism are discussed.

FROM THE AUTHORS' SUMMARY.

SHOCK DEATH WITH PERSISTENT THYMUS. HERBERT FACIUS, Med. Klin. **44**:902 (July 15) 1949.

The report concerns a 40 year old man who succumbed after an intravenous injection of 0.6 Gm. of neoarsphenamine given for syphilis. Smaller previous injections were well tolerated. On postmortem examination somewhat large lymphatic structures were found. The thymus weighed 30 Gm. It is felt that a status thymicolymphaticus may be of importance in cases of death after use of arsphenamine. Besides syphilis the patient had tuberculous lesions.

AMBERG, Rochester, Minn.

HYPOPHYSIS TRANSPLANTATION IN CASES OF DIABETES INSIPIDUS. HANS HORNBOSTEL, Med. Klin. **44**:996 (Aug. 5) 1949.

Two patients, 17 and 18 years of age, with idiopathic diabetes insipidus received transplants of fresh calf hypophysis. In one case the effect lasted four months; consequently a further transplantation is contemplated. In the other, the improvement has now persisted into the fourth month.

AMBERG, Rochester, Minn.

TREATMENT OF THE WATERHOUSE-FRIDERICHSEN SYNDROME. M. G. STRONK, Maandschr. v. kindergeneesk. **17**:121, 1949.

A description is given of an observed case of Waterhouse-Friderichsen syndrome successfully treated with an intravenous drip of cortical abstract, sulfadiazine in large amounts and penicillin. There is discussion of the question of to what extent the adrenal hemorrhage may be the cause of the accompanying shock, in relation to a causal therapy.

FROM THE AUTHOR'S SUMMARY.

Diseases of Muscles, Bones, Joints and Lymph Nodes

THE PATHOGENESIS AND SYMPTOMATOLOGY OF ACUTE INFLAMMATORY BONE DISEASES IN CHILDHOOD. WILHELM FALK, Ann pædiat. **173**:23 (July) 1949.

Falk reports on a toddler in whom, after frost damages of all three degrees on hands and legs, severe bone changes occurred. Every other illness that had to be considered from a diagnostic point could be excluded. Roentgenologically there was a severe degree of osteoporosis in the distal parts of both ulnas. On practically all the fingers and on the fifth metacarpal, on the basic phalanges of the fourth and fifth toes and on the fifth metatarsal there were dactylitic processes with periosteal thickening. Under symptomatic treatment only, complete healing of all the osseous changes occurred in a very short time. The severity and the speed with which the bone illness developed are explained by the infantile type of hyperergic reaction as to the circulatory damage caused by the frost.

FROM THE AUTHOR'S SUMMARY.

EWING SARCOMA AND BONE RETICULOSARCOMA. HANS R. SCHINZ, Bull. Schweiz. Akad. d. med. Wissensch. **5**:261 (July) 1949.

The reticulosarcoma of bones and the sarcoma of Ewing in the strict sense are biologically quite different sarcomas of the osteomyeloma. Their clinical aspect and prognosis differ as well. The sarcoma of Ewing begins with the symptoms of osteomyelitis and is roentgenographically characterized by an "onion skin" picture. The reticulosarcoma of bones has few clinical symptoms and roentgenologically resembles chronic osteomyelitis. The histiogenesis of both tumors is hypothetical. In the reticulosarcoma of bones the primitive cell may be the reticulocyte or the reticuloblast; in the sarcoma of Ewing it must be admitted that the primitive cell is unknown.

FROM THE AUTHOR'S SUMMARY.

HOW SHALL PERTHES' DISEASE BE TREATED? G. EXNER, Med. Klin. **44**:708 (June 3) 1949.

The importance of protection against overuse and weight bearing in the treatment of Perthes' disease for a sufficient length of time is emphasized.

AMBERG, Rochester, Minn.

LIPOCALCINOGRANULOMATOSIS—A NEW LIPOIDOSIS. ERICH ANDREAS, Med. Klin. **44**:913 (July 22) 1949.

The principal symptoms of lipocalcinogranulomatosis are painless and nearly always symmetrical tumors with characteristic roentgenograms. Microscopically cholesterol storage and deposits of calcium, together with degeneration of the tissue with formation of granulation tissue, are seen. The lesions are located in bursas and muscles. It is assumed that the disease is a real cholesterol storage disease only recently reported, and the accumulation of cholesterol was proved also by chemical analysis in a case of the condition which occurred in a 10 year old boy. It seems that it occurs in siblings.

AMBERG, Rochester, Minn.

VARIATIONS IN THE COURSE OF DEVELOPMENT OF OSSIFICATION CENTERS IN CHILDREN IN DIFFERENT REGIONS OF BOHEMIA. K. SILINK, Pediat. listy **4**:25, 1949.

In 412 roentgenograms of hands of school children with unfinished ossification from different regions of Bohemia, variations in the course of ossification of the carpal bones have been found in 28 per cent. The occurrence of the variation varies in different regions. The examination of the variations is important for the study of the genotypical structure of different population groups. (The occurrence varies between 24 and 33 per cent.) The frequency of the variations is more indirectly than directly related to the occurrence of endemic thyropathy and delayed ossification.

FROM THE AUTHOR'S SUMMARY.

SYNOSTOSIS HUMERORADIALIS. J. VESELSKY, Pediat. listy **4**:159, 1949.

A case in which a 6 year old girl had fixation of both elbow joints in flexion is described. The function of the upper extremities was good, and no other abnormality was observed.

FROM THE AUTHOR'S SUMMARY.

Diseases of the Eye

PERSISTENT HYALOID ARTERY WITH ABSENCE OF RETINAL VESSELS. R. BERNOULLI, Ophthalmologica **117**:169 (March) 1949.

In a 7 year old boy, a large reddish yellow band was seen to extend from the region of the disk to the posterior pole of the lens. The diagnosis was persistent hyaloid artery surrounded by a thickened glial sheath with many small vessels on the surface. There was complete absence of retinal vessels. The choroidal circulation was clearly visible. The combined occurrence of persistence of the hyaloid artery and absence of retinal vessels has been reported but once before (Magnus 1927). The author attempts to explain the genesis of this maldevelopment.

[ARCH. OPHTH.]

PHARMACOLOGICAL DATA AND FIRST RESULTS OF TREATMENT OF TUBERCULOUS EYE INFECTIONS WITH PARAAMINOSALICYLIC ACID. R. WITMER and L. RAGAZ, Schweiz. med. Wchnschr. **79**:452 (May 21) 1949.

Experiments were conducted on rabbits. On subconjunctival injections of 1 ml. of paraaminosalicylic acid in concentrations of 2.8 or 4 per cent surprisingly high concentrations were found in the anterior chamber of the eye, and nearly all in the free form. The concentration drops at first rapidly, but even after five hours considerably more than the necessary bacteriostatic limit is present. On peroral administration of 3.9 ml. of 20 per cent solution of paraaminosalicylic acid per kilogram (0.68 Gm. of paraaminosalicylic acid) rather high concentrations, particularly of total paraaminosalicylic acid, were found in the anterior chamber for six hours, while on a dose of 2.08 Gm. of paraaminosalicylic acid per kilogram effective concentrations were maintained for six hours. Only a few patients suffering from tuberculous uveitis were treated with aminacyl by mouth and subconjunctival injections every second day with encouraging results.

AMBERG, Rochester, Minn.

NEWER CONCEPTIONS OF THE GENESIS OF STRABISMUS. HANS-FELIX PIPER, Med. Klin. **44**:1307 (Oct. 14) 1949.

Various theories of strabismus in children are presented, and the conclusion is reached that a weakness of the cerebral cortex in relation to the subcortex is the causative factor.

AMBERG, Rochester, Minn.

A DIPTERA LARVA IN THE ANTERIOR CHAMBER OF THE EYE. ERICH HESSE, Wien. klin. Wchnschr. **61**:689 (Oct. 21) 1949.

A 12 year old boy came under observation on account of a severe iridocyclitis. On examination a wormlike motile larva could be seen above a hypopyon, which on removal proved to be the larva of a Hypoderma bovic (Oestridae).

AMBERG, Rochester, Minn.

FATE OF THE EYES IN 100 REEXAMINED CASES OF KERATITIS ECZEMATOSA. F. SCHWAB, Wien. klin. Wchnschr. **61**:719 (Oct. 21) 1949.

The author believes that an eczematous (or scrofulous) keratoconjunctivitis observed during childhood leaves local immunity of the eyes, perhaps also of the whole organism, so that severe tuberculous diseases of the eye occur only rarely.

AMBERG, Rochester, Minn.

Cutaneous Diseases; Allergy

THE ETIOLOGY AND TREATMENT OF SO-CALLED VARICELLIFORM SKIN ERUPTION (KAPOSI). INGVAR ALM, Ann. pædiat. **173**:197 (Oct.) 1949.

The author reports on a case of varicelliform skin eruptions (Kaposi) in a girl 6 months old. Herpes virus and Staphylococcus aureus were cultured from the contents of the vesicles. The staphylococci were resistant to sulfonamides and penicillin but sensitive to streptomycin. Soon

after the beginning of the streptomycin treatment the patient became afebrile, but the vesicles spread and a labial herpes developed rapidly, while the general health and the temperature remained uninfluenced. The obvious increase of the antistaphylococci titer during the course of the illness proves that in this case the staphylococci were of primary importance for the development of the particular morbid features.

FROM THE AUTHOR'S SUMMARY.

CATARACT AND CUTANEOUS POIKILODERMIC AFFECTIONS (SYNDROME OF ROTHMUND) AND OF THE SCLERODERMIC TYPE (SYNDROME OF WERNER). A. FRANCESCHETTI and G. MAEDER, Schweiz. med. Wchnschr. **79**:657 (July 23) 1949.

In four girls of a family of nine children cataracts developed rapidly during early childhood, while the cutaneous poikilodermic lesions (infantile poikilodermia "Zinnser") were noted in early infancy. This syndrome of Rothmund is contrasted with the syndrome of Werner, in which the cataract as well as the cutaneous lesion (diffuse sclerodermic) appears after puberty.

AMBERG, Rochester, Minn.

CALMEL DISEASES—AN ALLERGIC AFFAIR. T. BAUMANN, Schweiz. med. Wchnschr. **79**:725 (Aug. 13); 750 (Aug. 20) 1949.

The author describes four cases in which mild mercurous chloride and santonin were given as anthelmintics. In another case there was a reaction to merbromin.

According to Fanconi, the disease belongs to the allergic diseases (acute allergic reaction to mercurous chloride). It may be followed by a severe subacute course with continuous severe erythrodermia and may be further complicated by meningoencephalitic symptoms and a lipid nephrosis. The acute disease is characterized, according to Fanconi, by exanthems generalized glandular enlargement with or without splenic tumor, fever, eosinophilia and relative leukopenia. Two cases of acrodynia are referred to mercury sensitization; another to a primary grip infection. Acrodynia also, according to Fanconi, is regarded as a neuroallergic late reaction.

Infants and older children and adults are much less liable to mercury sensitization.

AMBERG, Rochester, Minn.

A NEW REMEDY FOR SCABIES. JOSEF SCHMITT, Med. Klin. **44**:990 (Aug. 5) 1949.

Eighty patients with scabies, among whom were 30 children, were treated with gamma hexachlorocylohexane in the form of an emulsion with excellent results.

AMBERG, Rochester, Minn.

A CONTRIBUTION TO THE STUDY OF ECTODERMOSIS PLURIOFICIELLE FIESSINGER-BAADER, TYPE I (STOMATOECTODERMOSIS). GEJZA CINOVSKY, Pediat. listy **4**:150, 1949.

A case in which twin girls had the same disease is described. Also, a girl 8 years old had formes frustes and the same disease of type I developed in her 6 year old sister. Twenty-four hours after treatment with penicillin (total amount 600,000 units), the temperature became normal, and on the seventh day desquamation appeared. Immediately after the recovery, she contracted chickenpox.

FROM THE AUTHOR'S SUMMARY.

CONGENITAL ECTODERMAL DYSPLASIA. S. VAN CREVELD and C. VAN WAALWIJK VAN DOORN, Maandschr. v. kindergeneesk. **16**:453, 1949.

The authors give a description of a case of the anhydrotic type of congenital ectodermal dysplasia and discuss the symptoms which may be present in this disease and the circumstances which may cause it. In the above mentioned nonhereditary case the mother had suffered from persistent herpes labialis during the first months of pregnancy.

FROM THE AUTHORS' SUMMARY.

Miscellaneous

POISONING FROM ASPIDIUM DRUGS. PER SELANDER, Ann. pædiat. **173**:259 (Oct.) 1949.

Selander describes the mode of action and the freakish toxicity of the vermicidal aspidium group. The pretreatment with bicarbonate recommended in English medical literature probably increases the absorption of the drugs and for this reason is dangerous. As the purgative, castor oil is very likely the most preferable. Two cases of fatal poisoning from extractum aspidium spinulosum are reported: a 4½ year old boy died after 2 Gm. and a 2 year old girl, after 1.5 Gm. The author warns against the use of these drugs for children.

FROM THE AUTHOR'S SUMMARY.

ADOPTION PROBLEMS. TORSTEN THYSELL, Ann. pædiat. **173**:267 (Oct.) 1949.

Adoption should never be undertaken without medical advice. Only a doctor can judge the risks of illness in a child who is for adoption. Mental deficiency and mental illness, epilepsy and psychopathy should be considered in the first place, as possible inheritable qualities. The majority of undesirable adoption cases concern mentally deficient children. All children intended for adoption should undergo thorough physical and mental examinations. The physician should be enabled to repeat his control examinations from time to time. The natural and the prospective parents should also undergo somatic and mental examinations. Adoption by a single woman should not be fostered without urgent reasons. The natural parents should give up all contact with the child they have given away for adoption.

FROM THE AUTHOR'S SUMMARY.

FIRST OBSERVATION OF A HEREDITARY TRANSMISSION FROM TWO DALTONIANS OF DIFFERENT TYPE. A. FRANCESCHETTI, Bull. Schweiz. Akad. d. med. Wissensch. **5**:227 (July) 1949.

After reviewing the known facts concerning the hereditary transmission of congenital red-green blindness, as well as the theory of Waaler, according to which the genes for the protanope and deuteranope types are not alleles but are located on different loci in the X chromosome, the author reports the first observation of siblings born to parents with different types of red-green blindness. The examination of this family has permitted him to confirm the theory, according to which the type of color blindness in the sons corresponds to that of the mother, while the daughters are phenotypically free, although they possess in both X chromosomes a gene for red-green blindness.

FROM THE AUTHOR'S SUMMARY.

THE MULTIPLE POSSIBILITIES OF AN ARTIFICIAL RADIOACTIVE ISOTOPE (Co^{60}) OF LONG LIFE IN SOLUTION FOR RAY THERAPY OF MALIGNANT TUMORS. J. H. MÜLLER, Schweiz. med. Wchnschr. **79**:547 (June 18) 1949.

Radioactive cobalt (Co^{60}) is used in liquid form as radiocobalt chlorine solution. Rubber balloons introduced by way of natural passages or artificially produced ones can be filled with such a solution. It emits a practically monochromatic radiation of high energy.

AMBERG, Rochester, Minn.

THE PHARMACOLOGIC PROPERTIES OF IRGAPYRIN, A NEW PREPARATION OF THE PYRAZOL SERIES. G. WILHELMI, Schweiz. med. Wchnschr. **79**:577 (June 25) 1949.

3,5-Dioxy-1,2-diphenyl-4-n-butyl pyrazolidin sodium is water soluble, with a p_H of 8.2. The solution can be injected. Pharmacologically this compound is about as active as aminopyrine and dissolves the latter, allowing the parenteral administration of large doses of aminopyrine. "Irgapyrin" is a mixture of this new drug (G 13871) and aminopyrine in equal parts. It is dispensed as a 30 per cent solution. For the pharmacologic data the paper has to be consulted.

AMBERG, Rochester, Minn.

THE ABSORPTION OF PENICILLIN ADMINISTERED BY AEROSOL. G. F. CODURI, Lattante **20**:334 (June) 1949.

For maximum absorption and therapeutic efficiency of penicillin administered by aerosol, the droplet size should be not less than 1 micron, the nasal rather than the oral route should be used and the dose should be 100,000 units each administration. Blood concentrations were found to become three times greater by the aerosol than by the intramuscular administration.

HIGGINS, Boston.

INTOXICATION OF THE INFANT WITH ANESTHESIN. HANS-WOLFGANG OCKLITZ, Med. Klin. **44**:806 (June 24) 1949.

Two infants received insufflation of the buccal cavity with ethylaminobenzoate (anesthesin®). The probable dose was within the maximal limits for infants, given by Pfaundler as 0.05 to 0.1 Gm. given internally. In both cases a methemoglobinemia developed rather rapidly and yielded promptly to treatment with thionine.

AMBERG, Rochester, Minn.

DETERMINATION OF THE SPECIFIC GRAVITY OF FLUIDS. JOHS KRUTZSCH, Med. Klin. **44**:1093 (Aug. 26) 1949.

A new method for the determination of the specific gravity of small amounts of fluid is described, the specific gravity of 1 to 2 ml. of test fluid with an accuracy of 2 per cent.

AMBERG, Rochester, Minn.

EXPERIMENTAL INVESTIGATIONS OF THE ACTION OF URETHANE IN WHITE RATS. K. VOIT and H. J. HODEIGE, Med. Klin. **44**:1115 (Sept. 2) 1949.

White rats received ethylurethane subcutaneously daily. The animals died after about 31 days. On postmortem examination an enlargement of the liver with necrotic areas and a greatly diminished spleen were found; in addition, usually bronchopneumonic areas. Nearly all the white rats, generally used for experimental purposes, are infected with a virulent Bartonella muris ratti and have a chronic infectious enlargement of the spleen. On extirpation of the spleen the latent infection is activated and produces the same lesions as in the urethane-treated rats. The lesions in these rats are due not to urethane as such but to the activation of the latent Bartonella infection induced by the damage to the spleen.

AMBERG, Rochester, Minn.

CLINICAL RESULTS OF ULTRASONICS. C. WIETHE, Wien. klin. Wchnschr. **61**:17 (Jan. 14) 1949.

The supersonic effects in biology are discussed. The treatment has been used in cases of otosclerosis and Ménière's disease with beneficial results. On the basis of experiments on young animals reported by Buchtala, special care is to be exercised with children.

AMBERG, Rochester, Minn.

PROPHYLACTIC PEDIATRICS. A. RUESS, Wien. klin. Wchnschr. **61**:639 (Oct. 7) 1949.

In his initial lecture as chief of the Children's Clinic of the University of Vienna, Ruess discusses some of the problems of prophylactic pediatrics, with attention to the accomplishments in Austria. Great stress is laid on the encouragement of breast feeding, as well as on the proper collection of human milk and the production of good cow's milk and milk products. The importance of specially trained nurses is strongly emphasized.

AMBERG, Rochester, Minn.

THE CEPHALIN-CHOLESTEROL TEST IN PEDIATRICS. JIRÍ HOMOLKA, Pediat. listy **4**:18, 1949.

The cephalin-cholesterol test and its evaluation in 91 cases of different diseases are described. If only a 4+ reaction is taken as a sign of disorder of the liver parenchyma, then the test agrees in 95.9 per cent of cases with the clinical findings. Lower grades of positivity should

be evaluated with care. This test is especially suitable for the evaluation in the cases of lighter liver disorder. In cases of more serious disorders the test is always fully positive and cannot, therefore, give more information. This higher sensitivity of the test is confirmed by a parallel examination by the Takata-Ara test in 15 cases. FROM THE AUTHOR'S SUMMARY.

PRECIPITATION CURVE OF THE WELTMANN REACTION IN PEDIATRICS. R. STRYCEK, Pediat. listy **4**:137, 1949.

The author describes a method of colorimetric reading of the Weltmann reaction. He characterizes the normal precipitation curve and describes the difference of its course in vitro and in vivo. FROM THE AUTHOR'S SUMMARY.

A NEW METHOD OF DIAGNOSTIC PUNCTURE OF THE SPLEEN AND LIVER. O. TEYSCHL, Pediat. listy **4**:144, 1949.

Teyschl presents a detailed description of an original method: A free and short needle is used, which is connected with a syringe by an elastic and strong catheter. The method was used in 26 cases without any incidents. FROM THE AUTHOR'S SUMMARY.

LUNG CHANGES AFTER DRINKING KEROSENE. J. J. SOER, Maandschr. v. kindergeneesk. **17**:118, 1949.

After the drinking of kerosene, apart from toxic symptoms, symptoms of disease referable to the lung appear. Very often these symptoms are determined only by roentgen examination, while in a physical examination practically nothing significant is found. The symptoms and signs disappear slowly. They consist of spots principally in the lower regions of the lungs.

FROM THE AUTHOR'S SUMMARY.

News and Comment

ANNOUNCEMENTS

Supplementary Edition of Motion Picture Reviews Now Available.—The Committee on Medical Motion Pictures of the American Medical Association has completed the first supplement to the second revised edition of the booklet entitled "Reviews of Medical Motion Pictures." This supplement contains 86 reviews of medical and health films reviewed in *The Journal of the American Medical Association* from Dec. 31, 1949 to Jan. 1, 1951. Each film has been indexed according to subject matter. The purpose of these reviews is to provide a brief description and an evaluation of motion pictures which are available to the medical profession.

Copies of this supplement are available upon request to:

The Committee on Medical Motion Pictures, American Medical Association, 535 North Dearborn Street, Chicago 10, Ill.

Continuation Course on Diseases of the Blood in Infancy and Childhood.—Dr. William Dameshek, Professor of Clinical Medicine, Tufts University School of Medicine, Boston; Clement A. Finch, Associate Professor of Medicine, University of Washington School of Medicine, Seattle, Wash., and Robert W. Heinle, Associate Professor of Medicine, Western Reserve University School of Medicine, Cleveland, will participate in a continuation course on Diseases of the Blood in Infancy and Childhood to be presented at the Center for Continuation Study April 16 to 18, 1951. The course is given under the direction of Drs. Irvine McQuarrie and Charles D. May, Department of Pediatrics, University of Minnesota.

PERSONAL

Award for Dr. Grulee.—On Jan. 31, 1951, at a luncheon at the Biltmore Hotel in New York, Clifford G. Grulee, M.D., was awarded a medal for "outstanding services to children" by the *Parents' Magazine*.

CORRECTION

In the article "Circulatory Diseases of the Kidneys in Infancy and Childhood: IV. Occlusion of the Renal Artery" by Drs. Wolf W. Zuelzer, Ruben Kurnetz and William A. Newton Jr., appearing in the January 1951 issue, the first sentence of the second paragraph on page 24 should read, "The autopsy disclosed thrombosis of the lower abdominal aorta," instead of "thrombosis of the liver and abdominal aorta."

Book Reviews

Alice in Motherland. By Carolyn B. Blish. Price, $1. Pp. 69, with illustrations. The Delaware State Society for Mental Hygiene, Wilmington, Del., 1949.

The object of this book is to help prospective parents, particularly from the psychologic angle, deal with the problems which arise in the home because of pregnancy and the presence of a new baby. To develop her theme, the author has taken the liberty of using Lewis Carroll's Alice, for her purpose now grown to womanhood, married and pregnant, as the central character in her narrative. Two adult-minded infant spirits from babyland, Sunshine and Gloomy, act as mentors instead of the White Rabbit. These agreeable personalities discuss with Alice and her husband the importance of full partnership throughout the momentous experience of pregnancy; the proper social attitudes on Alice's part; what the husband can do to help his wife through this period; the importance of avoiding worry; the advantages of "rooming-in" of the newborn baby; the attitudes of older children in the family toward the mother and the new baby; breast feeding; the procedure of "natural" childbirth, and other important information. Many of the chapters are followed by questionnaires by means of which the expectant mother may with some degree of accuracy check her own reactions to the various experiences of pregnancy. The booklet is delightfully written and beautifully illustrated and contains much highly sugar-coated good advice, but it lacks conciseness and is too "highbrow" to be enjoyed by most prospective mothers. It is a little difficult to picture any but graduate students in sociology or psychiatry getting the maximum that this charming presentation has to offer.

Introduction into the Modern Diagnosis of Congenital Angiocardiologic Conditions. By M. Grob and E. Rossi. Pp. 156, with 132 partially colored illustrations. Benno Schwabe, Klosterberg 27, Basel 10, Switzerland, 1949. Imported by Grune & Stratton, Inc., 381 4th Ave., New York 16.

This volume consists of nine articles published in the *Helvetica Acta Paediatrica*, with an introduction by G. Fanconi, Zurich. The first article, by M. Grob and E. Rossi, is a highly condensed presentation of the methods for the differential diagnosis of fifteen typical congenital disorders of the heart. The following methods are discussed: clinical findings at heart and lungs; complications; life duration; cause of death; electrocardiogram; phonocardiographic record; roentgen ray findings in the anteroposterior, left oblique and right oblique views; angiocardiogram (dextrogram, levogram); fluorescein time, needed for the determination of the circulation time, and catheterization of the heart, used for determination of the oxygen saturation and for the measurement of the intracardial pressure in the vena cava, right atrium, right ventricle and arteria pulmonalis. The findings are illustrated in sixty-eight diagrams. A table, 3 pages wide, with very instructive drawings summarizes the findings characteristic for the normal heart and for each of the various congenital malformations.

Max Holzmann summarizes in the second article the electrocardiographic findings characteristic for each of the fifteen types of congenital malformations of the heart. The Haldane-Barcroft method is recommended in the article, entitled "The Importance of the Gas Analysis in the Diagnosis of Congenital Heart," by C. Maier and M. Volkmann. A. Prader, E. Rossi and M. Wodenegg give a report on the results of determinations of plasma and blood volume in 20 cases of morbus caeruleus (blue babies) as compared with 23 healthy children. The authors used Geigy's blue method. "The Anomalies of the Aortic Arch and Its Branches with Special Reference to Their Embryologic Genesis," are described by M. Grob.

M. Grob and M. Stockmann discuss the "Isthmus Stenosis (Coarctation) of the Aorta," with a report on the results of surgical intervention. Clinical findings and autopsy results in rare malformations are discussed in two succeeding articles: E. de Chastonay and M. Buser describe the case of a 5½ month old infant in whom the left coronary artery originated from the pulmonary artery. E. Howald reports a case in which there was an anomalous opening of the pulmonary veins into the superior vena cava and another with an opening into the hepatic vein.

The last article, by W. Frischknecht, discusses the "Orthostatic Electrocardiogram in Children with Instability of the Vegetative Nervous System." This orthostatic electrocardiogram is to a large degree autonomous and independent of the other partial symptoms of a vegetative dystonia.

Summaries in English, French and Italian are given for the last seven of the nine articles. No summaries are given for the first two articles because, as the editor states, these articles are summaries in themselves.

These articles will be invaluable even to readers who have little or no knowledge of the German language, since the important facts are explained in drawings, in instructive figures and in graphs and since all expressions used are technical terms or Latin names which are understood internationally.

Talks to Parents and Teachers: Insight into the Problems of Childhood. By Homer T. Lane. Preface by A. S. Neill. Price, $2.75. Pp. 217. Hermitage Press, Inc., 8 E. 61st St., New York 21, 1949.

Homer Lane (1876-1925) was an American-born educator who developed a specialized interest in rehabilitation of delinquent youths and became director of a self-governing reformatory in England His experience with deviations in behavior led him to look for the causes in the early years of life. After a lapse of twenty-four years, several of his friends arranged to have the present selection from his writings and lectures published. At first thought it might well be supposed that this volume would be of historical interest only, but the truth is that time has had no effect on the relevancy of Lane's thinking. The principles of preventive mental hygiene are expressed as clearly here as by the writers of today. One even finds a well supported plea for "demand feeding" of infants (page 45).

Early in the book the author states: "The attitude of the enlightened parent should be one of reverence and trust in the nature of the child, who is always working at some unfulfilled wish" (page 40). The main theme of the book is that children are born with creative instincts or drives which are too often cramped and thwarted by adult authority and misinterpretation, with harmful effects on the child's personality development. The premium many parents place on "good" behavior stifles creative urges and replaces them with desires for approval and possessive pleasures.

Pediatricians will enjoy reading this book, even though they will not agree with all the author proposes, for it is well written and challenging. As it is not a manual on the rearing of children, it should be read before it is recommended to parents. It is an excellent book for a couple awaiting their first child, and it should also prove useful in families in which parental authority is too rigid. The author, however, has given little recognition to the part parents' own emotional instabilities and psychiatric problems play in disturbed parent-child relationships, and the simple recommendation of this book in such situations, without additional help, would probably increase the basic difficulties. It would also be an unwise suggestion for parents who have been known to "experiment" with different theories about the rearing of children. A sudden shift to a "child-centered family" when there is no judgment concerning the proper time to redirect the child's impulses would be an ordeal for everyone.

Teachers should read this book, since the principles expressed by the author are quite in agreement with trends in education today.

The author seldom enters the field of physical development, for his training is not in this direction. There are a few statements about physical health which are not generally accepted, as, for example, "If, however, there is violent dependence and fixation on the mother, then faulty teeth are grown" (page 60). There are but few instances of this and they are easily recognized.

Acute Laryngotracheobronchitis. By A. Harry Neffson, M.D. Price, $5. Pp. 197, with 17 illustrations. Grune & Stratton, Inc., 381 4th Ave., New York 16, 1949.

This small volume is meaty and concise and carries the reader into a broader field than its title might imply, into problems associated with respiratory obstruction. It is well written and easy to read and is based on wide experience.

The author doubts a specific causation of this disease but considers virus infection most important. Pathologic aspects, both ante and post mortem, are adequately described. Especially valuable is the careful attention to detail in treatment. The author emphasizes the prevention of complications after tracheotomy by first securing a free airway and then proceeding to operation without unnecessary dissection of fascial planes—a previously recognized contribution of the author.

There is an excellent discussion on the causes of emphysema and pneumothorax and their relation to infection and to operation.

One might wish that greater consideration had been given to the pathophysiologic involvement developing from purely mechanical factors, but the volume gives fairly the current concept of the diseases. On the basis of recent studies indicating the usual presence of excess carbon dioxide in respiratory obstruction, one might question the advice for the inhalation of this agent to liquefy secretions.

Audiology—The Science of Hearing: A Developing Professional Specialty. By Norton Canfield, M.D. Price, $1.75. Pp. 59. Charles C Thomas, Publisher, 301-327 E. Lawrence Ave., Springfield, Ill., 1949.

This small monograph discusses in general terms the departments concerned and the function of each in discovery and rehabilitation of the deafened under nearly ideal conditions. The author outlines the part played by the physician, particularly the otologist, the acoustic physicist, the neuropsychiatrist, the members of the speech department and the social service workers in a properly organized center.

Directory of Pediatric Societies *

INTERNATIONAL

International Pediatric Association

President: Dr. Felix Hurtado, Habana, Cuba.

Secretary: Dr. Guido Fanconi, Kinderklinik, Zurich, Switzerland.

Next Meeting (Seventh International Congress of Pediatrics): Habana, Cuba, 1953.

International Congress for the Protection of Infancy

Secretary: Prof. G. B. Allaria, Corso Bramante 29, Torino 120, Italy.

Pan American Congress of Pediatrics

President: Dr. Felix Hurtado, Habana, Cuba.

International Union for Child Welfare

President: Mrs. Gordon Morier.

Secretary: Dr. Georges Thélin, 43 Quay Wilson, Geneva, Switzerland.

FOREIGN

Argentine Pediatric Society of Buenos Aires

President: Dr. Martin Ramón Arana, 1809 Rodriquez Peña, Buenos Aires.

General Secretary: Dr. Alfredo Larguia, Cerrito 1179, Buenos Aires.

Associação Paulista de Medicina, Secção de Pediatrias

President: Dr. Armando de Arruda Sampaio.

First Secretary: Dr. Luis Fontoura y Lauro Machado Oliveira, Caixa Postal 2103, São Paulo, Brazil.

Second Secretary: Dr. Luiz Augusto Monteiro Toledo, Av. Brigadeiro Luiz Antonio 393, 1° Andar, São Paulo, Brazil.

Time: Twelfth of every month, 8:30 p. m.

Asociación Pediatrica de Guatemala

President: Dr. Carlos Manuel Monzon, Plazuela Santuario de Guadalupe, Guadalupe.

Secretary: Dr. Maria Isabel Escobar, Casa del Niño no. 1, Guadalupe.

British Paediatric Society

President: Dr. A. G. Maitland-Jones.

Secretary: Dr. Alan Moncrieff, Institute of Child Health, Hospital for Sick Children, Great Ormond St., London W. C. 1.

Place: Windermere.

Bulgarian Pediatric Society

President: Dr. L. Ratchew, University Children's Hospital, Wassil Kolarow 46, Sofia.

Chinese Pediatric Society

President: Dr. Fu-tang Chu, Peking Children's Hospital, Peking, China.

Secretary: Dr. Hua-kang Chow, Peking Union Medical College, Peking, China.

Time: Concurrent with the annual conference of the Chinese Medical Association.

Czechoslovak Pediatric Society

Chairman: Prof. Dr. Jiri Brdlík, 2 Sokolská, Prague II.

Danish Pediatric Society

Chairman: Prof. Preben Plum.

Secretary: Dr. Elin Fog, Søllingsvey 17, Charlottenlund, Denmark.

* Secretaries of societies are requested to furnish the information necessary to make this list complete and to keep it up to date.

German Pediatric Society

President: Dr. H. Kleinschmidt.
Secretary: Dr. F. Goebel, 5 Moorenstrasse, Düsseldorf, Germany (British Zone).

Hellenic Society of Pediatrics

President: Dr. C. Saroglou, Patission St. 74, Athens, Greece.
Secretary-General: Dr. S. Charocopos, Alexandras Ave. 1, Athens, Greece.

Indian Pediatric Society

President: Dr. K. C. Chaudhuri, Dept. of Pediatrics, Medical College, Calcutta.
Secretary: Dr. S. P. Bhattacharjee, Dept. of Pediatrics, Medical College, Calcutta.
Place: Office of the Indian Medical Association, 67 Dharamtala St., Calcutta 13.
Time: Every second and fourth Wednesday of each month.

Medical Association of Israel, National Pediatric Society

President: Prof. L. F. Meyer, 29 Idelson St., Tel-Aviv, Israel.
Secretary: Dr. W. Hirsch, Hadassah Municipal Hospital, Tel-Aviv, Israel.

Nederlandsche Vereeninging voor Kindergeneeskunde

President: Dr. G. J. Huët, 39 Brediusweg, Bussum.
Secretary: Dr. H. Reerkink, % Sophia Kinderziekenhuis, 160 Gordelweg, Rotterdam.
Place: Children's Hospital or Pediatric Clinic. Time: Three times a year.

Palestine Jewish Medical Association, Section of Physicians of Children's Diseases

See Medical Association of Israel, National Pediatric Society.

Pediatric Society of New Zealand

President: Dr. Lawrence Ludbrook, The Lister Building, Victoria Street East, Auckland.

Royal Society of Medicine, Section for the Study of Diseases in Children

President: Dr. Kenneth Tollerman.
Secretary: Dr. I. M. Anderson; Dr. Ronald MacKeith.
Place: 1 Wimpole St., London W. 1. Time: Fourth Friday of each month, 4:15 p. m.

Schweizerische Gesellschaft für Pädiatrie

President: Prof. Dr. A. Hottinger, Petersplatz 12, Basel.
Secretary: Dr. F. Hauser, Kinderspital, Basel.

Sociedad Boliviana de Pediatria

President: Dr. Carlos Ferrufino, Casilla 272, La Paz, Bolivia.
Secretary: Dr. Cecilio Abela D., Casilla 272, La Paz, Bolivia.
Place: S. C. I. S. P. Bldg. Time: Every Thursday.

Sociedad Chihuahuense de Pediatria

President: Dr. Carlos Villamar Talledo.
Vice President: Dr. H. Uranga.
Secretary: Dr. Reynaldo Ramos Varela.
Treasurer: Dr. David Russek.
Place: Children's Hospital, Matamoros St., Chihuahua, Chihuahua, Mexico.

Sociedad Chilena de Pediatria

President: Dr. Miguel Fabres Izaga.
Secretary-General: Dr. Oscar Undurraga A., Merced 565, Santiago, Chile.
Place: Medical Society, Merced 565, Santiago, Chile. Time: 7 p. m., every Thursday.

Sociedad Cubana de Pediatria

President: Prof. Agustin Castellanos.
Secretary: Dr. Carlos Hernandez Miyares, Hospital Nuestra Señora de las Mercedes L y 21. Apartado 2430, Habana.
Place: Cátedra de Clinica Infantil, Hospital Nuestra Señora de las Mercedes y Hospital Municipal de Infancia, Habana. Time: 9 p. m., last Wednesday of every month.

SOCIEDAD DOMINICANA DE PEDIATRIA

President: Dr. Jaime Jorge, Jose Joaquin Perez, no. 25, Ciudad Trujillo, R.D.
Secretary-Treasurer: Dr. Alberto Peguero, V., Ave. Bolivar 113, P. O. Box 464, Ciudad Trujillo, R.D.
Place: Children's Ramfis Hospital. Time: 8 p. m., last Friday of every month.

SOCIEDAD ECUATORIANA DE PEDIATRIA

President: Dr. Alfredo Ceballos Carrión.
Secretary: Dr. Rafael Compte Andrade, P. O. Box 3480, Guayaquil.
Place: Hospital Central. Time: 11:30 a. m., every Friday.

SOCIEDAD MEXICANA DE PEDIATRIA

President: Dr. Roberto L. Sanchez.
Secretary: Dr. Luis Torregrosa F.
Place: Hospital Infantil. Time: Last Thursday of every month.

SOCIEDAD DE PEDIATRÍA DE CONCEPCIÓN (CHILE)

President: Dr. Raúl Ortega A., Hospital Clínico Regional, Concepción.
Secretary: Dr. Fidel Urrutia, Hospital Clínico Regional, Concepción.
Place: Hospital Clínico Regional, Concepción. Time: 7:30 p. m., second Tuesday of every month from April to December, inclusive.

SOCIEDAD DE PEDIATRÍA DE CÓRDOBA

President: Dr. Juan Francisco Herrera, Córdoba, Argentina.
Secretary: Dr. Albino F. Dottori, Dean Fumes 2000, Esq. Ocaña (N.), Córdoba, Argentina.
Place: Comite pro Defenso del Niño, Dean Fumes 2000, Córdoba, Argentina.
Time: Once a month.

SOCIEDAD DE PEDIATRIA DEL LITORAL

President: Dr. Jose E. Celoria, Hospital Centenario, Rosario, Argentina.
Secretary: Dr. Gloria Lovell, Hospital Centenario, Rosario, Argentina.

SOCIEDAD DE PEDIATRÍA DE SANTIAGO DE CUBA

President: Dr. Antonio Béguez César, Sagarra 107, Santiago de Cuba.
Secretary: Dra. Susana Texdó Vaillant, Padre Pico 57, Santiago de Cuba.
Place: Colegio Médico. Time: Last Tuesday of every month.

SOCIEDADE PORTUGUÊSA DE PEDIATRIA

President: Prof. Castro Freire.
Secretary-Generale: Dr. Cordeiro Ferreira, Hospital de D. Estefania, Lisbon, Portugal.

SOCIEDAD URUGUAYA DE PEDIATRIA

President: Dr. Conrado Pelfort.
Secretary: Dr. José M. Portillo.
Place: Club Medico del Uruguay, Avenida Agraciada 1464 (Piso 13), Montevideo.

SOCIEDAD VENEZOLANA DE PUERICULTURA Y PEDIATRIA

President: Lya Imber Coronil.
Secretary: Dr. Guillermo Tovar, P. O. Box 5, Caracas.
Place: Hospital Municipal de Niños, Caracas. Time: Once a month.

SOCIEDAD YUCATECA DE PEDIATRIA

President: Dr. José Lavalle, Yucatan, Mexico.
Secretary: Dr. Francisco Solís, Yucatan, Mexico.
Place: Hospital del Niño, Yucatan, Mexico.

SOCIÉTÉ DE PÉDIATRIE DE MONTRÉAL

President: Dr. Paul Letondal, 370 E. Roy St., Montreal, Quebec, Canada.
Secretary-Treasurer: Dr. Edmond Baril, 301 Carré Saint-Louis, App. 1, Montreal, Quebec, Canada.
Time: First and Third Thursday of each month.

SOCIÉTÉ DE PÉDIATRIE DE PARIS

President: Dr. G. Heuyer, 1 Ave. Emile Deschanel, Paris 7e, France.
Secretary: Dr. Maurice Lamy, 94 rue de Varenne, Paris 7e, France.
Place: Hôpital des Enfants Maladies, 149 Rue de Sèvres. Time: 4:30 p. m., third Thursday of each month.

SOCIETÉ POLONAISE DE PÉDIATRIE

President: Dr. Jan Bogdanowicz, Dzialdowska 1, Warsaw.
Secretary: Dr. Zofia Leimbach, Mieroslawskiego 9 m.6, Warsaw.

SOUTH AFRICAN PAEDIATRIC ASSOCIATION

Chairman: Dr. Basil Melle, 89 Lister Bldg., 195 Jeppe St., Johannesburg, South Africa.
Secretary-Treasurer: Dr. Seymour Heymann, 17 Lister Bldg., 195 Jeppe St., Johannesburg, South Africa.

SWEDISH ASSOCIATION OF PEDIATRICS

President: Prof. Sture Siwe, Lund.
Secretary: Dr. K. A. Melin, Färjestadsvägen 16, Bromma.

SWEDISH MEDICAL SOCIETY, SECTION FOR PEDIATRICS AND SCHOOL HYGIENE

President: Docent H. Magnusson, Sachs' Hospital for Children, Stockholm.
Secretary: Dr. M. d'Avignon, Norrtulls Sjukhus, Stockholm.
Place: Swedish Medical Society, Klara Östra Kyrkogata 10, Stockholm and Pediatric Clinic Upsala. Time: Second Friday of each month (except summer).

VIENNA PEDIATRIC SOCIETY

President: Prof. Dr. A. Solé, Karolinen-Kinderspital, Sobieskigasse 31, Vienna 9.
Secretary: Doz. Dr. Asperger, Universitäts-Kinderklinik, Lazarettgasse 14, Vienna 9.

NATIONAL

AMERICAN MEDICAL ASSOCIATION, SCIENTIFIC ASSEMBLY, SECTION ON PEDIATRICS

Chairman: Dr. Woodruff L. Crawford, 321 W. State St., Rockford, Ill.
Secretary: Dr. Margaret Mary Nicholson, 1801 Eye St. N. W., Washington, D. C.

AMERICAN ACADEMY OF PEDIATRICS

President: Dr. Paul W. Beaven, 26 S. Goodman St., Rochester 7, New York.
Secretary: Dr. Clifford G. Grulee, 636 Church St., Evanston, Ill.
Annual Meeting: Place: Toronto, Canada. Time: Oct. 20-25, 1951.*

AMERICAN HOSPITAL ASSOCIATION, MASSACHUSETTS HOSPITAL ASSOCIATION

Chairman: Dr. Frank Wing, Boston.
Secretary: Dr. W. Franklin Wood, McLean Hospital, Waverly 79, Mass.

AMERICAN PEDIATRIC SOCIETY

President: Dr. Valjean Cooke, 8700 Argyle Ave., St. Louis.
Secretary-Treasurer: Dr. Henry G. Poncher, 1819 W. Polk St., Chicago 12.

CANADIAN SOCIETY FOR THE STUDY OF DISEASES OF CHILDREN

President: Dr. P. E. Williams, 193 James St. S., Hamilton, Ontario.
Secretary-Treasurer: Dr. R. L. Denton, 1615 Cedar Ave., Montreal.

SOCIETY FOR PEDIATRIC RESEARCH

President: Dr. Henry H. Gordon, 4200 E. 9th Ave., Denver 7, Colo.
Secretary-Treasurer: Dr. Robert Ward, Bellevue Hospital, New York 16.
Place: French Lick, Ind. Time: 1950.

SECTIONAL

INTERMOUNTAIN PEDIATRIC SOCIETY

President: Dr. Spencer Snow, 75 S. Main St., Salt Lake City.
Secretary-Treasurer: Dr. Esther Gross, 202 E. South Temple St., Salt Lake City.
Place: Salt Lake City General Hospital. Time: First Thursday of each month, 8 p. m.

* The time and place of this meeting were incorrectly given in the January issue.

NEW ENGLAND PEDIATRIC SOCIETY

President: Dr. Henry E. Gallup.
Secretary-Treasurer: Dr. Harry Shwachman, 300 Longwood Ave., Boston.
Time: Four meetings a year.

NORTH PACIFIC PEDIATRIC SOCIETY

President: Dr. Gordon O. Matthews, 808 Medical-Dental Bldg., Vancouver, B. C.
Secretary-Treasurer: Dr. S. Gorham Babson, 1220 S. W. Taylor St., Portland, Oregon.

NORTHWESTERN PEDIATRIC SOCIETY

President: Dr. Paul Bancroft, 909 Sharp Bldg., Lincoln, Neb.
Secretary-Treasurer: Dr. Northrop Beach, 1009 Nicollet Ave., Minneapolis.
Place: Minneapolis, St. Paul, Duluth and Rochester. Time: January, April, July and October.

ROCKY MOUNTAIN PEDIATRIC SOCIETY

President: Dr. Joseph Lyday, 227 16th St., Denver 2.
Secretary-Treasurer: Dr. Edwin T. Williams, 1850 Gilpin St., Denver 6.
Place: Children's Hospital of Denver or the Colorado General Hospital. Time: Monthly from October to June.

SOUTHERN MEDICAL ASSOCIATION, SECTION OF PEDIATRICS

Chairman: Dr. Carroll M. Pounders, 1200 N. Walker St., Oklahoma City.
Secretary: Dr. Samuel F. Ravenel, 371 N. Elm St., Greensboro, N. C.

SOUTHWESTERN PEDIATRIC SOCIETY

President: Chester I. Mead, 1930 Truxton Ave., Bakersfield, Calif.
Secretary: Dr. Clement H. Molony, 416 N. Bedford Dr., Beverly Hills, Calif.
Place: University Club of Los Angeles. Time: 6:30 p. m., second Wednesday in January, March, May, September and November.

STATE

ALABAMA PEDIATRIC SOCIETY

President: Dr. W. A. Daniel Jr., 115 S. Union St., Montgomery 5, Ala.
Secretary-Treasurer: Dr. D. B. Monsky, 905 Norman Bridge Rd., Montgomery 6, Ala.

ARIZONA PEDIATRIC SOCIETY

President: Dr. Carl A. Holmes, 1401 N. 7th Ave., Phoenix.
Secretary-Treasurer: Jacob M. Sobol, 607 Heard Bldg., Phoenix.
Place: Phoenix or Tucson. Time: On Call.

ARKANSAS STATE PEDIATRIC ASSOCIATION

Chairman: Dr. C. B. Billingsley, 1425 N. 11th St., Fort Smith.
Secretary: Dr. R. E. Weddington, 1425 N. 11th St., Fort Smith.

CALIFORNIA STATE MEDICAL SOCIETY, SECTION ON PEDIATRICS

Chairman: Dr. Alice Potter, 1418 Ninth Ave., San Francisco 22.
Secretary: Dr. Carl Erickson, 595 E. Colorado, Pasadena.

FLORIDA STATE PEDIATRIC SOCIETY

President: Dr. Edgar W. Stephens, 910 Harvey Bldg., West Palm Beach.
Secretary: Dr. Hugh A. Carithers, 2000 Park St., Jacksonville 4.
Place: Concurrent with state association convention and fall meeting.

GEORGIA PEDIATRIC SOCIETY

President: Dr. Howard J. Morrison, 444 Drayton St., Savannah.
Secretary-Treasurer: Dr. J. Harry Lange, 490 Peachtree St. N. E., Atlanta.
Place: Atlanta. Time: At time of annual state meeting.

HEZEKIAH BEARDSLEY PEDIATRIC CLUB OF CONNECTICUT

President: Dr. H. L. F. Locke, 179 Allyn St., Hartford, Conn.
Secretary: Dr. L. W. Minor, 119 Main St., Middletown, Conn.

ILLINOIS STATE MEDICAL SOCIETY, SECTION ON PEDIATRICS

Chairman: Dr. Eugene T. McEnery, 4458 W. Madison St., Chicago 24.
Secretary: Dr. George L. Drennen, Jacksonville, Ill.

INDIANA STATE PEDIATRIC SOCIETY

President: Dr. K. T. Knode, 1105 E. Jefferson Bldg., South Bend.
Secretary-Treasurer: Dr. Matthew Winters, 621 Hume Mansur Bldg., Indianapolis.
Time: Two meetings a year.

IOWA PEDIATRIC SOCIETY

President: Dr. Charlotte Fisk, 1201 Equitable Bldg., Des Moines 9.
Secretary-Treasurer: Dr. James Dunn, Davenport Bank Bldg., Davenport.

LOUISIANA STATE PEDIATRIC SOCIETY

President: Dr. William C. Rivenbank, 1448 Louisiana Ave., New Orleans 15.
Secretary-Treasurer: Dr. Bertha Wexler, 3439 Prytania St., New Orleans 15.

MEDICAL SOCIETY OF THE STATE OF NEW YORK, PEDIATRIC SOCIETY

Chairman: Dr. Thurman B. Givan, 115 Remsen St., Brooklyn 2.
Secretary: Dr. Reginald A. Higgons, Port Chester.

MEDICAL SOCIETY OF THE STATE OF PENNSYLVANIA, PEDIATRIC SECTION

Chairman: Dr. Waldo E. Nelson, Temple University, Philadelphia 40.
Secretary: Dr. Carl C. Fischer, 100 W. Coulter St., Philadelphia 44.

MICHIGAN STATE MEDICAL SOCIETY, PEDIATRIC SECTION

Chairman: Dr. Robert J. Mason, 308 N. Woodward Ave., Birmingham, Michigan.
Secretary: Dr. Horace L. French, 301 Seymour Ave., Lansing, Michigan.

MISSISSIPPI STATE PEDIATRIC SOCIETY

President: Dr. Harvey F. Garrison Jr., 315 E. Capitol Place, Jackson.
Secretary: Dr. Guy Verner, 126 N. Congress St., Jackson.

MONTANA PEDIATRIC SOCIETY

President: Dr. Edward A. Hagmann, 208 N. Broadway, Billings, Montana.
Secretary: Dr. George W. Nelson, 2814 9th Ave. N., Billings, Montana.
Place: Decided at each meeting—Spring and Fall.

NEBRASKA PEDIATRIC SOCIETY

President: Dr. George E. Stafford, 823 Sharp Bldg., Lincoln, Neb.
Secretary-Treasurer: Dr. Donald C. Nilsson, 115 North 40 Street, Omaha, Neb.
Place: Children's Memorial Hospital. Time: Third Thursday of each month from October to June, inclusive. Dinner at 6 p. m.

NEW HAMPSHIRE PEDIATRIC SOCIETY

President: Dr. Edward L. Tuohy, Manchester.
Secretary-Treasurer: Dr. William D. Penhale, Concord.

NEW JERSEY MEDICAL SOCIETY, PEDIATRIC SECTION

Chairman: Dr. Israel J. Wolf, 231 E. 31st St., Paterson.
Secretary: Dr. N. T. Crane, 147 E. 7th St., Plainfield, N. J.

NEW MEXICO STATE PEDIATRIC SOCIETY

President: Dr. M. K. Wylder, 221 W. Central Ave., Albuquerque.
Secretary-Treasurer: Dr. Ly Werner, 221 W. Central Ave., Albuquerque.

NORTH CAROLINA PEDIATRIC SOCIETY

President: Dr. Jean Craven, 19 W. Third St., Lexington, N. C.
Secretary-Treasurer: Dr. Susan C. Dees, Duke Hospital, Durham, N. C.

NORTHERN CALIFORNIA PEDIATRIC SOCIETY

President: Dr. William C. Deamer, 3 Fifth Ave., San Francisco 18.
Secretary: Dr. A. L. Gleason, 1066 Longridge Rd., Oakland 10.
Place: San Francisco. Time: Second Thursday of February, April, September and November.

NORTH DAKOTA PEDIATRIC SOCIETY

President: Dr. R. E. Dyson, Northwest Clinic, Minot, N. D.
Secretary-Treasurer: Dr. William J. Ball, Northwest Clinic, Minot, N. D.
Place: Fargo Clinic, Fargo, N. D. Time: October 15.

OKLAHOMA STATE PEDIATRIC SOCIETY

President: Dr. J. B. Snow, 625 N. W. 10th St., Oklahoma City.
Secretary: Dr. Bertha Levy, 1200 N. Walker St., Oklahoma City.
Place: With Oklahoma State Medical Association. Time: Annual Meeting.

PHILIPPINE PEDIATRIC SOCIETY

President: Dr. Alberto V. Tupas, Philippine General Hospital, Manila, Philippines.
Secretary: Dr. Artemio P. Jongco, Philippine General Hospital, Manila, Philippines.
Place: Philippine General Hospital. Time: Every two months.

SOUTH CAROLINA PEDIATRIC SOCIETY

President: Dr. B. Owen Ravenel, 95 Rutledge Ave., Charleston 16.
Secretary-Treasurer: Dr. John R. Harvin, 206 N. Sumter St., Sumter.

TENNESSEE PEDIATRIC SOCIETY

President: Dr. W. O. Vaughan, 2103 Hayes St., Nashville 5.
Secretary-Treasurer: Dr. C. Barton Etter, 1678 Peach, Memphis 12.
Place: Chattanooga. Time: Second Monday in April.

TEXAS PEDIATRIC SOCIETY

President: Dr. Thomas D. McCrummen, 304 Capitol Nat'l Bank Bldg., Austin, Texas.
Secretary: Dr. M. C. Carlisle, 1410 Austin Ave., Waco, Texas.
Treasurer: Dr. Edith Bonnet, 228 Medical Arts Bldg., San Antonio, Texas.

VIRGINIA PEDIATRIC SOCIETY

President: Dr. E. Berkeley Neal.
Vice President: Dr. E. L. Kendig.
Secretary-Treasurer: Dr. W. A. Mitchell.
Executive Board: Dr. F. R. Hopkins and Dr. J. O. Rydeen.

WEST VIRGINIA STATE MEDICAL SOCIETY, SECTION ON PEDIATRICS

President: Dr. K. J. Winters, 1411 Wauwatosa Ave., Milwaukee 13, Wis.
Secretary: Dr. Niels L. Low, 744 Main St., Racine, Wisconsin.

WISCONSIN STATE MEDICAL SOCIETY, SECTION ON PEDIATRICS

Chairman: Dr. M. G. Peterman, 411 E. Mason St., Milwaukee 2.
Secretary: Dr. L. M. Simonson, 1001 N. 8th St., Sheboygan.

LOCAL

ACADEMY OF MEDICINE OF CLEVELAND, PEDIATRIC SECTION

Chairman: Dr. Charles H. York, 10465 Carnegie Ave., Cleveland 6.
Secretary: Dr. Earl E. Smith, 10640 Carnegie Ave., Cleveland 6.
Place: Allen Memorial Medical Library. Time: 8:15 p. m., October, December, February and April.

ACADEMY OF MEDICINE, TORONTO, SECTION OF PEDIATRICS

President: Dr. A. L. Chute, 170 St. George St., Toronto, Canada.
Secretary: Dr. John Fletcher, 262 St. Clair St. W., Toronto, Canada.
Place: Academy of Medicine. Time: 8:30 p. m., third Thursday of each month.

BALTIMORE CITY MEDICAL SOCIETY, PEDIATRIC SECTION

Chairman: Dr. J. Edmund Bradley, University Hospital, Baltimore 1.
Secretary: Dr. Wilson Grubb, 4 E. 33rd St., Baltimore 18.

BRONX PEDIATRIC SOCIETY

President: Dr. Nathan M. Greenstein, 1488 Metropolitan Ave., New York.
Secretary: Dr. George Weiss, 790 Grand Concourse, New York 51.
Place: Morrisania City Hospital. Time: 8:30 p. m., second Wednesday of each month, except June, July, August and September.

Brooklyn Academy of Pediatrics

President: Dr. Lewis A. Koch, 62 Pierrepont St., Brooklyn.
Secretary: Dr. Stanley S. Lamm, 20 Plaza St., Brooklyn 17.
Place: Granada Hotel. Time: 8:45 p. m., fourth Wednesday of February, March, April, October and November.

Buffalo Pediatric Society

President: Dr. Douglas P. Arnold, 159 Bidwell Parkway, Buffalo, N. Y.
Secretary: Dr. Richard A. Downey, 786 Forest Ave., Buffalo 9, N. Y.
Place: Children's Hospital, 219 Bryant St. Time: 8:30 p. m., first Monday of each month from September to June.

Central New York Pediatric Club

President: Dr. T. Wood Clarke, 7 Cottage Place, Utica, N. Y.
Secretary-Treasurer: Dr. Fred W. Bush, 11 N. Goodman St., Rochester, N. Y.
Place: Various cities in New York. Time: Third Tuesday of April and October.

Central Ohio Pediatric Society

President: Dr. E. H. Baxter, 327 E. State St., Columbus, Ohio.
Secretary-Treasurer: Dr. E. V. Turner, 2479 E. Main St., Columbus, Ohio.
Place: As Announced. Time: On call.

Chicago Pediatric Society

President Dr. Alvah L. Newcomb, 723 Elm St., Winnetka, Ill.
Secretary: Dr. Alfred S. Traisman, 6349 N. Clark St., Chicago.
Place: Children's Memorial Hospital, 710 Fullerton Ave. Time: Third Tuesday of each month, October to May inclusive.

Cincinnati Pediatric Society

President: Dr. John H. Hunt, Kemper Lane Bldg., Cincinnati.
Secretary: Dr. William F. Hunting, 6048 Montgomery, Cincinnati.
Place: Children's Hospital, Elland Ave., Cincinnati. Time: On call.

Dade County Pediatric Society

President: Dr. William W. McKibben, 641 N. Greenway Drive, Coral Gables, Fla.
Secretary-Treasurer: Dr. Wesley S. Nock, 671 N.E. 57th St., Miami 38, Fla.
Time and Place: Variable.

Dallas Pediatric Society

President: Dr. Guy Hacker, 5711 Goliad St., Dallas.
Secretary-Treasurer: Dr. George R. Branch, 4325 Cole Ave., Dallas.
Place: Children's Hospital of Texas and Bradford Memorial Hospital. Time: 1 p. m., third Saturday and 8:30 p. m., the first Tuesday of each month.

Detroit Pediatric Society

President: Dr. Wilfred D. H. Nolting, 16840 E. Warren, Detroit.
Secretary: Dr. Ruben Meyer, 938 Maccabees Bldg., Detroit.
Place: Variable. Time: Five times annually.

Fort Worth Pediatric Society

President: Dr. Frank Cohen, 712 S. Henderson, Fort Worth, Texas.
Secretary: Dr. H. H. Womack, 1422 Pennsylvania, Fort Worth, Texas.
Place: Welch and West Restaurant. Time: Third Friday of each month.

Honolulu Pediatric Society

President: Dr. Walter B. Herter, 305 Royal Hawaiian Ave., Honolulu.
Secretary-Treasurer: Dr. Teruo Yoshina, 1221 Victoria St., Honolulu 14.
Place: At doctors' homes in rotation. Third Thursday of each month, 6 p. m.

Houston Pediatric Society

President: Dr. Byron P. York, 3911 Montrose Blvd., Houston, Texas.
Secretary: Dr. David Schrum, 3207 Montrose Blvd., Houston, Texas.
Place: River Oaks Country Club. Time: 7:30 p. m., fourth Tuesday of each month.

Kansas City (Missouri) Pediatric Society

President: Dr. Harry M. Gilkey, 1624 Professional Bldg., Kansas City.
Secretary: Dr. Leland Speer, 1022 Hoel Parkway, Kansas City.
Place: Kansas City General Hospital. Time: On call.

KNOXVILLE-OAK RIDGE PEDIATRIC SOCIETY

President: Dr. Henry S. Christian, 205 Medical Arts Bldg., Knoxville, Tenn.
Secretary: Dr. John Eggleston, Oak Ridge Hospital, Oak Ridge, Tenn.

LOS ANGELES COUNTY MEDICAL ASSOCIATION, PEDIATRIC SECTION

President: Dr. Elena Boder, 1830½ Lucille Ave., Los Angeles 26.
Secretary-Treasurer: Dr. Robert Simonds, 267 S. Beverly Dr., Beverly Hills, Calif.
Place: Los Angeles County Medical Association Bldg., 1025 Wilshire Blvd. Time: Second Monday of February, April, June, October and December.

MEDICAL SOCIETY OF THE COUNTY OF KINGS AND THE ACADEMY OF MEDICINE OF BROOKLYN, PEDIATRIC SECTION

President: Dr. Jacob Rosenblum, 161 Rugby Rd., Brooklyn.
Secretary: Dr. Irving Weinstock, 350 Ocean Ave., Brooklyn.
Place: Kings County Medical Society. Time: 8:45 p. m., fourth Monday of April, October, November, January and March.

MEDICAL SOCIETY OF THE DISTRICT OF COLUMBIA, SECTION ON PEDIATRICS

President: Dr. John Washington, 2032 Belmont Rd. N. W., Washington, D. C.
Secretary-Treasurer: Dr. George Maksim, 1418 Good Hope Rd. S. E., Washington, D. C.
Place: Medical Society Bldg., 1718 M St. N. W. Time: Spring and fall.

MEMPHIS PEDIATRIC SOCIETY

President: Dr. C. Barton Etter, 1678 Peach, Memphis 12, Tenn.
Secretary-Treasurer: Dr. Jacob Danciger, 188 S. Bellevue Blvd., Memphis 4, Tenn.
Place: University Center, 4 S. Dunlap. Time: 7 p. m., second Tuesday of every month.

MILWAUKEE PEDIATRIC SOCIETY

President: Dr. A. L. Kastner, 1810 West Wisconsin Ave., Milwaukee 3, Wis.
Secretary-Treasurer: Dr. A. L. Babbitz, 606 West Wisconsin Ave., Milwaukee 3, Wis.
Place: City Club of Milwaukee. Time: Second Wednesday in February, April, June, October and December.

NASHVILLE PEDIATRIC SOCIETY

President: Dr. John M. Lee, Doctors Bldg., Nashville, Tenn.
Secretary: Dr. Dan S. Sanders Jr., 2103 Hayes St., Nashville, Tenn.
Time: Third Thursday of every month.

NEW YORK ACADEMY OF MEDICINE, SECTION ON PEDIATRICS

Chairman: Dr. Arthur F. Anderson, 122 E. 76th St., N. Y., N. Y.
Secretary: Dr. L. Emmett Holt Jr., 477 First Ave., N. Y., N. Y.
Place: New York Academy of Medicine, 2 E. 103rd St. Time: Second Thursday of each month from November to May, inclusive, 8:30 p. m.

OKLAHOMA CITY PEDIATRIC SOCIETY

President: Dr. Bertha M. Levy, 717 N. W. 22d St., Oklahoma City 3.
Secretary: Dr. C. M. Bielstein, 301 N. W. 12th St., Oklahoma City 3.
Place: Oklahoma Club. Time: On call.

PHILADELPHIA PEDIATRIC SOCIETY

President: Dr. T. F. McNair Scott, 1740 Bainbridge St., Philadelphia 46, Pa.
Secretary: Dr. F. H. Harvie, 133 S. 36th St., Philadelphia 4.
Place: College of Physicians, 19 S. 22nd St. Time: 8:30 p. m., second Tuesday from October to May, inclusive.

PITTSBURGH PEDIATRIC SOCIETY

President: Dr. J. A. Gilmartin, 3708-15th Ave., Pittsburgh.
Secretary-Treasurer: Dr. C. J. Stoecklein, Medical Arts Bldg., Pittsburgh 13.
Place: Municipal Hospital, Pittsburgh. Time: Second Friday in October, December, February and April.

QUEENS PEDIATRIC SOCIETY

President: Dr. Harold T. Vogel, 34-20, 86 St., Jackson Heights, N. Y.
Secretary: Dr. Moe Goldstein, 111-32, 76th Ave., Forest Hills, L. I.
Place: Forest Hills, N. Y. Time: Third Monday of October 1950, February and April 1951, and first Monday of December 1950.

Richmond Pediatric Society

President: Dr. Thomas S. Chalkley, 421 W. Grace St., Richmond 20, Va.
Secretary-Treasurer: Dr. John Paul Jones, 810 W. Franklin St., Richmond 20, Va.
Place: Medical College Hospital. Time: 8 p. m., third Thursday of each month, except June, July and August.

Rochester Pediatric Society

President: Dr. Jerome Glaser, 85 San Gabriel Dr., Rochester 10, N. Y.
Secretary-Treasurer: Dr. Daniel B. Peeler, 1162 Lake Ave., Rochester 13, N. Y.
Place: Rochester Academy of Medicine or arrangement by program committee. Time: Third Friday of each month from October to May.

St. Louis Pediatric Society

President: Dr. Donald L. Thurston, 500 S. Kingshighway, St. Louis 10.
Secretary-Treasurer: Dr. Leo F. Gowan, 337 W. Lockwood Ave., St. Louis 19.
Place: Candlelight House. Time: Second Thursday of each month from October to May, inclusive, 6:30 p. m.

San Antonio Pediatric Society

President: Dr. Lucius Hill, 328 Medical Arts Bldg., San Antonio 5.
Secretary-Treasurer: Dr. Edith M. Bonnet, 228 Medical Arts Bldg., San Antonio 5.
Place: Bexar County Medical Library. Time: 7:30 p. m., first Tuesday of every month.

Santa Barbara Pediatric Society

President: Dr. Helen Hart, City Health Department, de la Guerra Plaza, Santa Barbara, Calif.
Vice President: Dr. Clarence Hills, 22B W. Micheltorena St., Santa Barbara, Calif.
Secretary-Treasurer: Dr. L. C. N. Wayland, 1235 Chapala St., Santa Barbara, Calif.
Meetings: Four times annually.

Seattle Pediatric Society

President: Dr. David M. Harris, Medical Arts Bldg., Seattle 1.
Secretary: Dr. William A. Jaquette Jr., 1305 Seneca, Seattle 1.
Place: College Club. Time: Fourth Friday of each month from September to June at 6:30 p. m.

University of Michigan Pediatric and Infectious Disease Society

President: Dr. Ernest H. Watson, University Hospital, Ann Arbor.
Secretary: Dr. Harry A. Towsley, 1313 E. Ann St., Ann Arbor.

Waco Pediatric Society

President: Dr. F. William Hoehn, 1422 Austin Ave., Waco, Texas.
Secretary: Dr. J. M. Garrett, 1408 Austin Ave., Waco, Texas.
Place: Providence Hospital, 1725 Colcord, Waco, Texas. Time: Third Thursday of each month.

Westchester County Medical Society, Pediatrics Section (New York)

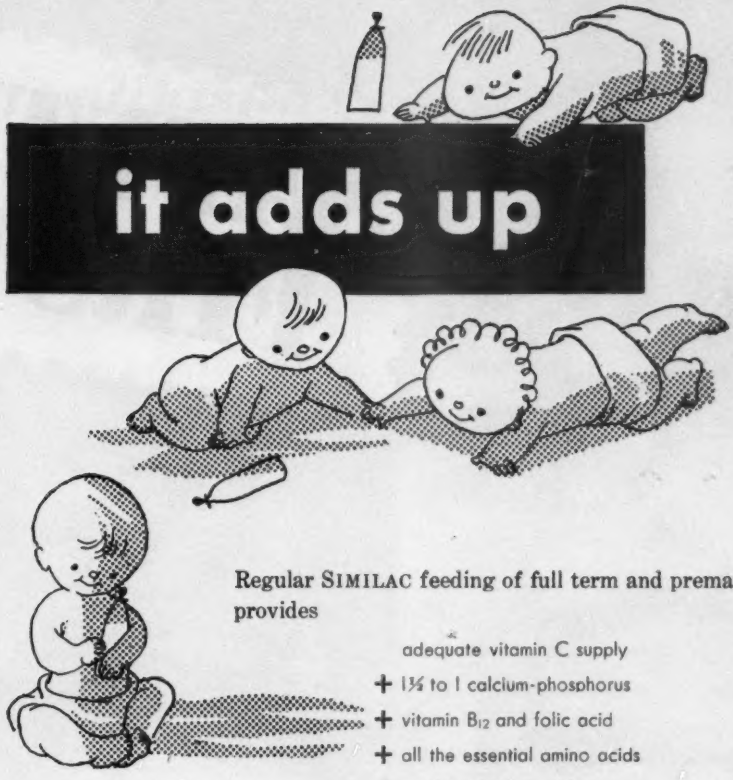
President: Dr. Harry W. Kaessler, 147 Prospect Ave., Mount Vernon, N. Y.
Secretary-Treasurer: Dr. Elvira Ostlund, 64 Highland Rd., Rye, N. Y.
Place: The Roger Smith Hotel, White Plains, N. Y. Time: Fourth Thursday of every other month from September to June (dinner meetings).

Western Michigan Pediatric Society

President: Dr. Horace L. French, 301 Seymour Ave., Lansing, Michigan.
Secretary-Treasurer: Dr. John C. Montgomery, 1810 Wealthy St. S. E., Grand Rapids, Michigan.
Time: Meets on the first Wednesday in October, November, April and May of each year. Two meetings are held in Grand Rapids and two in other designated localities.

Wichita Pediatric Society

President: Dr. Walter L. Schafer, 401 N. Emporia St., Wichita 2, Kan.
Secretary: Dr. William F. McGuire, 401 N. Emporia St., Wichita 2, Kan.
Place: Variable: Time: First Thursday of each month.



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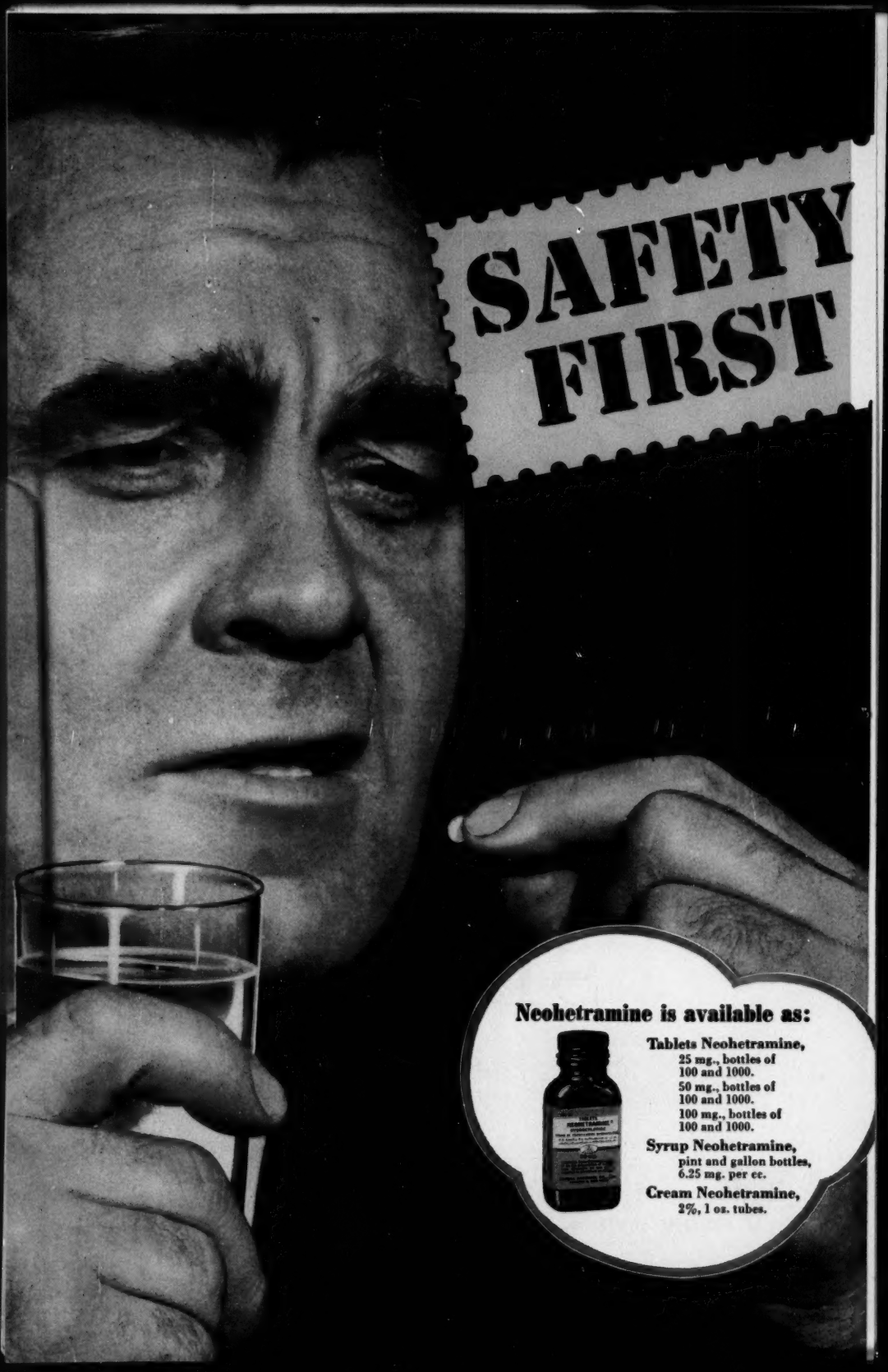
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References: 1. Alexander, H. L.: Postgrad. Med. 3:278 (April) 1948. 2. Bernstein, J. B., and Feinberg, S. M.: J. Allergy 19:393 (Nov.) 1948. 3. Criep, L., and Aaron, T. H.: J. Allergy 19:215 (July) 1948. 4. Friedlaender, S. M., and Friedlaender, A. S.: J. Lab. & Clin. Med. 33:865 (July) 1948. 5. Schwartz, E.: Ann. Allergy 5:770 (Nov.-Dec.) 1949.

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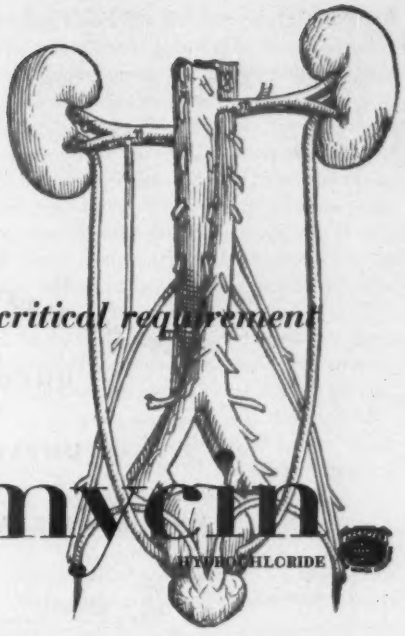

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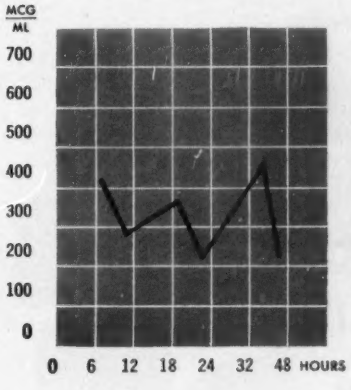
concentration of Terramycin in the urine following divided oral doses: 0.5 Gm. q 6 h.[3]



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1. Schoenbach, E. B.; Bryer, M. S., and Long, P. H.: Ann. New York Acad. Sc. 53:245 (Sept. 15) 1950.
2. Welch, H.; Hendricks, F. D.; Price, C. W., and Randall, W. A.: J. A. Ph. A. (Sc. Ed.) 39:185 (Apr.) 1950.
3. Welch, H.: Ann. New York Acad. Sc. 53:253 (Sept. 15) 1950.

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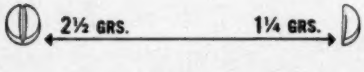

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applying the sum of today's knowledge

1. Hazard, S.; Smith, Clement A., and Denton, F.: *J. Pediat.* 38:18, 1951
2. LaDriere, R. J., and Burke, R. R.: To be published.

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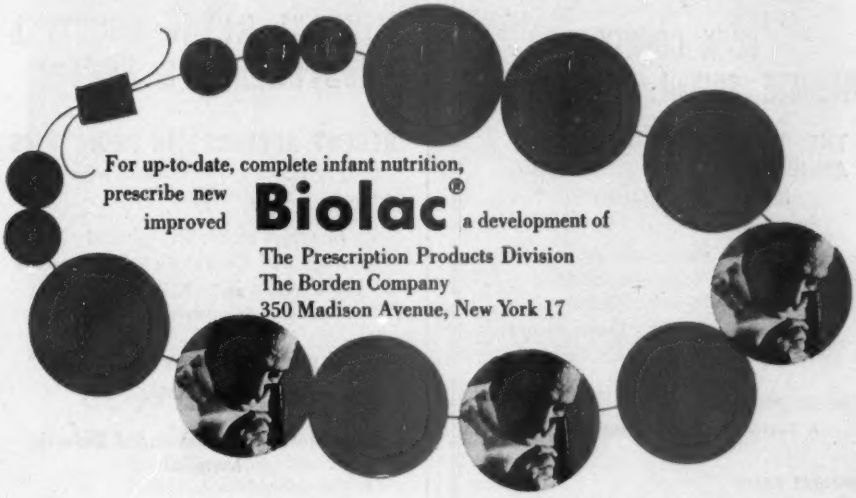

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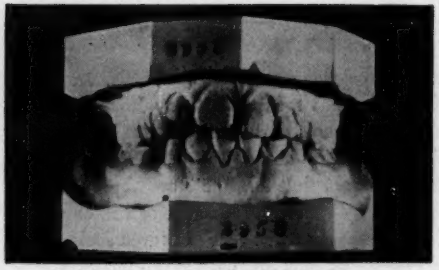

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Hand of above patient shows deformity caused by biting on finger. Note callous over joint and rotated tip of finger.

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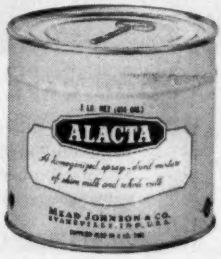

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Professional full-size samples and literature available on request. Write to the BIB Corporation, P.O. Box 866-N, Lakeland, Florida.

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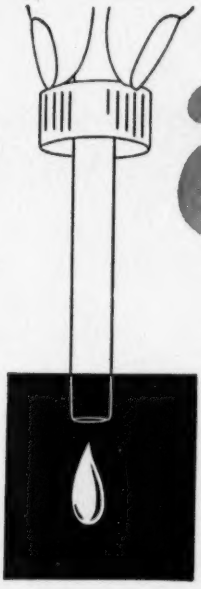
Doctors Prescribe Bib . . . Mothers Prefer Bib . . . Babies Love Bib

Available at leading baby food departments. Flash-Pasteurized, packed in individual feeding 4-ounce sterilized containers.

THE BIB CORPORATION • LAKELAND, FLORIDA

Dispersible
DRISDOL®
WITH
VITAMIN A

COMPLETELY
Milk
Diffusible



a+d

Drisdol with Vitamin A administered in milk becomes an integral part of the child's diet. It diffuses completely in milk, orange juice and other liquids without an oily film, does not separate, float or tend to adhere to nursing bottle or nipple. May also be given on the tongue or in solid foods.

Drisdol with Vitamin A contains per gram 50,000 units of vitamin A and 10,000 units of crystalline vitamin D_2 (calciferol). Each drop delivers 1250 vitamin A units and 250 vitamin D units.

Dosage for infants, 2 drops; for older children and adults, from 4 to 6 drops daily in milk.

Supplied in bottles of 10 cc. and 50 cc. with dropper.

Also Drisdol in Propylene Glycol (10,000 units of vitamin D_2 per gram) in bottles of 5 cc., 10 cc. and 50 cc.

To help build a sound structure and promote growth

Drisdol, trademark reg. U. S. & Canada, brand of crystalline vitamin D_2 (calciferol)

Winthrop-Stearns INC.
NEW YORK, N. Y. WINDSOR, ONT.